FORMULATION AND EVALUATION OF PREDNISOLONE SODIUM PHOSPHATE ORALLY DISINTEGRATED TABLETS

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CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF PREDNISOLONE SODIUM PHOSPHATE ORALLY DISINTEGRATED TABLETS**"submitted by **ELMUZAMIL ABBKER ELHAJ BAKHEET (26107707)** in partial fulfillmentof the degree of Master of Pharmacy in Pharmaceutics of The TamilNadu Dr.M.G.R Medical University, Chennai at Annai Veilankanni's Pharmacy College, Chennai- 600 015 is the Bonafide work carried out by his/her under my guidance and supervision during the academic year 2011-2012. The dissertation or any part of this has not been submitted elsewhere for any other degree.

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DECLARATION

I hereby declare that the dissertation work entitled "**FORMULATION AND EVALUATION OF PREDNISOLONE SODIUM PHOSPHATE ORALLY DISINTEGRATED TABLETS**" is based on the original work carried out by me in Annai Veilankanni's Pharmacy College, Saidapet, Chennai and Formulation R&D, Scoat pharmaceutical Pvt Ltd., Hyderabad under the guidance of **Dr. M.Senthil Kumar** and coguidance of **Mr.J.Subba reddy ,** for submission to The Tamilnadu Dr.M.G.R University in the partial fulfillment of the requirement for the award of degree Master of Pharmacy in Pharmaceutics. The work is original and has not been submitted in part or full for any other diploma or degree of this or any other university. The information furnished in this dissertation is genuine to the best of my knowledge and belief.

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INTRODUCTION

Tablets

Tablets may be defined as solid pharmaceutical dosage forms containing drug substances with or without suitable diluents and prepared either by compression or molding methods. They have been in widespread use since the latter part of the 19th century and their popularity continues. The term compressed tablet is believed to have been first used by "JOHN WYETH and Brother of PHILADELPHIN". During the same period molded tablets were introduced to be used as Hypodermic tablets for injections.

Tablets remain popular as oral dosage form because of the advantages, afforded both to the manufacturer [e.g.: simplicity & economy of preparation, stability and convenience in packing, shipping, and dispensing] and the patient [e.g.: accuracy of dosage, compactness, post ability, blandness of taste and ease of administration.

Although tablets are more frequently discoid in shape, they also may be round, oval, oblong, cylindrical or triangular. They may differ greatly in size and weight depending on the amount of drug substance present and the intended method of administration.

Properties of tablets

The attributes of an acceptable tablet are as follows:

- The tablet must be sufficiently strong and resistance to shock and abrasion and to withstand handling during manufacturing, packaging, shipping and use. Hardness and friability tests measure this property.
- Tablet must be uniform in weight and in drug content of the individual tablet. This is measured by the weight variation and content uniformity tests.
- The drug content of the tablet must be bioavailable. This property is measured by the dissolution test. Accurate bioavailability can be obtained from the drug levels of the drug after its administration.
- Tablets must be elegant in appearance and must have characteristic shape, color and other markings necessary to identify the product.
- Tablets must retain all these functional attributes, which include drug stability and efficacy.

Advantages of Tablets:

- They are easy to be administered
- They offer the greater capabilities of all oral dosage forms for the greatest dose precision and the least content variability.
- Their cost is lowest of all oral dosage forms.
- They are the lightest and most compact of all oral dosage forms.
- Product identification is potentially the simplest and cheapest, requiring no additional processing steps when employing an embossed or monogrammed punch face.
- They are in general the easiest and cheapest to package and ship of all oral dosage forms.
- They may provide the greatest ease of swallowing with the least tendency for "hang-up" above the stomach.
- They lend themselves to certain special release profile products, such as enteric or delayed release products.
- They are better suited to large-scale production than other unit oral forms.
- They have the best-combined properties of chemical, mechanical and microbiological stability of all the oral forms.
- One of the major advantages of tablet over capsules is that the tablet is essentially "tamperproof dosage form".

Disadvantages of Tablets:

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.
- Drugs with poor wetting, slow dissolution properties, intermediate to large dosages, or any combination of these features may be difficult or impossible to zormulate and manufacture as a tablet that will still provide adequate or full drug bioavailability.

- Bitter tasting drugs, drugs with objectionable odor or drugs that the sensitive to oxygen or atmosphere moisture may require encapsulation or a special type of coating with may increase the most of the finished tablets.
- A major disadvantage of capsules over tablets is their higher cost.

Types of tablets

Tablets are classified according to their route of administration or function. The following are the 5 main classification groups:

- **Tablets ingested orally**
    1. Compressed tablets
    2. Multiple compressed tablets
    3. Multilayered tablets
    4. Sustained action tablets
    5. Enteric coated tablets
    6. Sugar coated tablets
    7. Film coated tablets
    8. Chewable tablets
- **Tablets used in the oral cavity**
    1. Buccal tablets
    2. Sublingual tablets
    3. Lozenge tablets and torches
    4. Dental cones
- **Tablets administered by other routes**
    1. Implantation tablets
    2. Vaginal tablets
- **Tablets used to prepare solutions**
    1. Effervescent tablets
- **Molded tablets or tablet triturates (TT)**
    1. Dispensing tablets (DT)
    2. Hypodermic tablets (HT)

Compressed tablets:

These tablets are uncoated and made by compression of granules. These tablets are usually intended to provide rapid disintegration and drug release. These tablets

contain water-soluble drugs, which after swallowing get disintegrated in the stomach, and its drug contents are absorbed in the gastrointestinal tract and distribute in the whole body.

Multiple compressed tablets (MCT):

These tablets are prepared to separate physically or chemically incompatible ingredients or to produce repeat action prolonged action products. To avoid incompatibility, the ingredients of the formulation except the incompatible materials are compressed into a tablet then incompatible substances along with necessary excipients are compressed tablet.

Multilayered tablets:

These tablets consist of two or more layer of materials compressed successively in the same tablets. The color of each layer may be the same or different. The tablets having layers of different colors are known as "multicolored tablets".

Sustained action tablets:

These tablets are used to get a sustained action of medicament. These tablets when taken orally release the medicament in a sufficient quantity as and when required maintaining the maximum effective concentration of the drug in the blood through out the period of treatment.

Enteric-coated tablets (ECT):

These are compressed tablets meant for administration by swallowing and are designed to bypass the stomach and get disintegrated in the intestine only. These tablets are made to release the drug undiluted and in the highest concentration possible within the intestine. e.g.: tablets containing antihelmentics and amoebicides.

Sugar coated tablets (SCT):

The compressed tablets having a sugar coating are called "sugar coated tablets". Such coatings may be colored and are beneficial in covering up drug substances processing objectionable tastes or odors and protecting materials sensitive to oxidation.

Film coated tablets (FCT):

These are compressed tablets that are covered with a thin layer or a film of water-soluble material. A number of polymeric substances with film-forming properties may be used. Film coating imparts the same general characteristics as sugar coating, with the added advantage of greatly reduced time period required for the coating operation and reduced thickness of coating, these compressed tablets having some polymer substance, such as hydroxy propyl cellulose, hydroxy propyl methylcellulose and ethyl cellulose.

Chewable tablets:

These tablets are to be chewed in the mouth and broken into small pieces. In this way, the disintegration time is reduced and the rate of absorption of he medicament is increased. e.g.: aluminum hydroxide tablets, and phenolphthalein tablets.

Buccal tablets:

These tablets are to be placed in the buccal pouch or between the gums and lips or cheek where they dissolve or disintegrate slowly and are absorbed directly without passing into the alimentary canal. e.g.: tablets of ethisterone

Sublingual tablets:

These tablets are to be placed under the tongue where they dissolve or disintegrate quickly and are absorbed directly without passing into GIT. E.g.: tablets of glyceryl trinities.

Lozenges and torches:

These tablets are designed to exert local effect in the mouth or throat. These tablets are commonly used to treat sore throat or to control coughing in common cold. They may contain local anaesthetics antiseptic, antibacterial agents, astringent and antitussives.

Dental cones:

These are relatively minor compressed tablets meant for placing them in the empty socket after tooth extraction. They prevent the multiplication of bacteria in the socket following such extraction by using slow releasing antibacterial compounds or to

reduce bleeding by containing the astringent. These cones generally get dissolved in 20 to 40 min time.

Implantation tablets:

These tablets are placed under the skin or inserted subcutaneous by means of minor surgical operation and are slowly absorbed. These implants must be sterile and should be packed individually in sterile condition. Implants are mainly used for administration of hormones such as testosterone, and deoxycorticosterone etc.

Vaginal tablets:

These tablets are meant to dissolve slowly in the vaginal cavity. These tablets are typically ovoid or pear shaped to facilitate retention in the vagina. This tablet form is used to release steroids, antibacterial agents, antiseptics or astringents to treat vaginal infections.

Effervescent tablets:

In addition to the drug substance, these contain sodium bicarbonate and an organic acid such as tartaric acid or citric. In the presence of water, these additives react, liberating carbon dioxide that acts as disintegrator and produces effervescence. Except for small quantities of lubricants present, effervescent tablets are soluble.

Tablet triturates

Tablet triturates usually are made from moist material, using a triturate mold that gives them the shape of cut sections of cylinder. Such tablets must be completely and rapidly soluble. The problem arising from the compression of these tablets is the failure to find a lubricant that is completely water-soluble.

Dispensing tablets:

These tablets provide a convenient quality of potent drug that can be incorporated readily in to powders and liquids, thus circumventing the necessity to weigh small quantities. These tablets are supplied primarily as a convenience for extemporaneous compounding and should never be dispensed as a dosage form.

Hypodermic tablets:

Hypodermic tablets are soft, readily soluble tablets and originally were used for the preparation of solutions to be injected. Since stable parenteral solutions are now

available for most new drug substances, there is no justification for the hypodermic tablets for injection. Their use in this manner should be discouraged, since the resulting solutions are not sterile. Large quantities of these tablets continue to be made, but for oral administration. No hypodermic tablets ever have been recognized by the official compendia.

Tablets and hard gelatin capsules constitute a major portion of drug delivery systems that are currently available. However, many patient groups such as the elderly, children and patients who are mentally retarded, uncooperative, nauseated, or on reduced-liquid-intake diets have difficulty in swallowing these dosage forms. Elderly patients may find the administration of these dosage forms particularly difficult because many of them are required to consume medicines on a regular basis to maintain their quality of life. Children also may have difficulty ingesting these dosage forms because of their underdeveloped muscular and nervous systems. Swallowing conventional tablets can be further hindered by conditions such as allergic reactions, and episodes of coughing[1].

The aforementioned problems can be solved by developing rapidly disintegrating and dissolving tablet dosage forms for oral administration because they dissolve in saliva and do not require water for swallowing. Oral disintegrating tablets are also called as 'mouth dissolving tablets', 'orodispersible tablets', quick disintegrating tablets, rapid dissolving tablets, porous tablets and rapimelts[2].

Recently orally disintegrating tablet terminology has been approved by United States Pharmacopoeias, Centre for Drug Evaluation and Research (CDER).

US FDA defined orally disintegrating tablet as 'A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue'. Recently European pharmacopoeia also adopted the term 'orodispersible tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing[3]. Despite various terminologies used, orally disintegrating tablets are here to offer unique form of drug delivery with many advantages over the conventional dosage forms.

ORALLY DISINTEGRATE TABLETS:

Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop orally disintegrate tablets (ODT) with improved patient compliance and convenience. ODTs are solid unit dosage forms, which disintegrate or dissolve rapidly in the mouth without the need of chewing and water. It is particularly meant for people who have difficulty in swallowing conventional tablets and capsules. It has been reported that Dysphasia (difficulty in swallowing) is common among all age groups and more specific with pediatric and geriatric populations along with institutionalized patients and patients with nausea, vomiting, and motion sickness complications. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population[1].

Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablets that disperse readily and within 3 min in mouth before swallowing.

USFDA defined ODT as "*A solid dosage form containing medical substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue".* The disintegration time for ODTs generally ranges from several seconds to about a minute.

Typically a dispersible tablet is dispersed in about 5-15 ml of water (e.g. in a tablespoonful or a glass of water) and the resulting dispersion is administered to the patient. However, they can also be placed directly on the tongue and sucked. Dispersible tablets are required to disintegrate within 3 mins in water at 15-25°C. Also the dispersion produced from a dispersible tablet should pass through a sieve screen with a nominal mesh aperture of 710 microns. The dispersion properties of dispersible tablets can be facilitated by the inclusion of an acid/base couple in which the base liberates carbon dioxide when the components of the couple are dissolved in water.

Ideal characteristics of dispersible tablets

- They require water or other liquid at the time of administration.
- Should easily disintegrate and dissolve.
- Mask or overcome unacceptable taste of drug.
- They should have high drug loading.
- They should have pleasant feel in the mouth.
- They should have low sensitivity against environmental conditions like moisture, temperature etc.
- Ease of administration for patients who are mentally ill, disabled and uncooperative.
- Should be portable without fragility concern.
- They should be manufactured using conventional tablet processing and packaging equipment at low cost.

Special features of dispersible tablets

- Dispersible tablets are not intended to be chewed or swallowed whole. They should not be dispersed in carbonated drinks or milk due to foaming or slow dispersion. The purpose of dispersible tablet is to provide a unit dosage form of medication which can be easily administered to infants and children or to elderly, who may have difficulty swallowing a tablet intact.

Advantages of dispersible tablets

- They are particularly suitable both for elderly persons with swallowing difficulties and for children.
- Rapid disintegration and absorption of drug, which will produce quick onset on action.
- Certain dispersible tablets can also be divided.
- The bitter taste of the active substance must be masked in advance.
- Owing to the number of possible applications, the patient compliance is improved.

- These are convenient to carry, easy to manufacture and more stable.
- Quick absorption from the gastrointestinal tract improves bioavailability and reduces unwanted effects caused by the drug. e.g. gastrointestinal irritation caused by nonsteroidal anti inflammatory drugs.
- New business opportunities like product differentiation, line extension and life cycle management. Exclusivity of product promotion.
- Although chewable tablets have been on the market for some time, they are not same as the new dispersible tablets. Patients for whom chewing is difficult or painful can use these new tablets easily. Dispersible tablets can be used easily in children who have lost their primary teeth, but do not have full use of their permanent teeth.

Limitation of dispersible tablets

- One common limitation of these formulations is settling of the insoluble solids at the bottom or sides of container of the prepared dispersion, which may lead to a loss of part of the drug during administration, resulting in suboptimal dosing.

Disadvantages of dispersible tablets

- Most dispersible tablets lack the mechanical strength common to traditional tablets. Many products are very light weight and fragile requiring them to be individually packaged. Patients should be advised not to push these tablets through the foil film, but instead, peel the film back to release the fast dissolving tablet.
- Due to the formulation of dispersible tablets which also more susceptible to degradation via temperature and humidity. Some of the newest dispersible tablet formulations are dispensed in a conventional stock bottle. Pharmacists are advised to take care when dispensing such formulations to ensure they are exposed to high levels of moisture or humidity. Excess handling of tablets can introduce enough moisture to initiate dissolution of the tablet matrix.

Developmental challenges in dispersible drug delivery

- ***Ease of administration***

  Fast Dissolving Delivery Systems are easy to administer and handle hence, leads to better patient compliance. Usually, elderly people and pediatrics experience difficulty in swallowing the conventional dosage forms (tablets, capsules, solutions and suspensions) because of tremors of extremities and dysphasia. Fast Dissolving Delivery Systems may offer a solution for these problems.

- **Taste of the active ingredient**

  Some drugs have relatively no taste, and simply adding a suitable flavor can hide any unpleasant sensation. However, most drugs do require taste masking if they are to be incorporated into dispersible formulations. Numerous methods exist to achieve this, including simple wet granulation or roller compression with other excipients to minimize the presented surface area of the drug. Spray drying can also be employed to shroud the drug. If further taste masking is needed, the resultant particle can be sealed with a suitable coating material (like hydroxypropyl methyl cellulose, ethylcellulose, methacrylate and polyvinylpyrollidone). The choice of coating material will determine the mechanism of taste masking. In addition, the quantity of coat applied, how it is applied, and where other excipients are included in the coating will all affect the quality of taste masking.

  Cyclodextrins (cyclic linked oligosaccharides) have been shown to prove some measure of taste masking by trapping the drug within the cyclic structure long enough to render initial dissolution. Other taste masking methods namely coating methods including electrochemical, hot melt and supercritical fluids. Encapsulation using coacervation has also been employed to encapsulate certain drugs.

- **Dose**

  Molecules requiring high doses present challenges to development of dispersible dosage forms: 1) Taste masking of active ingredient, 2) mouth-feel or grittiness

and 3) tablet size. These challenges are not unrelated because most drugs will require taste masking. It depends on the degree of bitterness relative to the dose of the drug, which will in turn effect the final tablet size. As mentioned previously, drug may require coating, which will result in an increase in the particle size. The extent to which this increase will affect the mouth feel and tablet size will depend on the dose of the drug and the amount of coating material required masking its taste.

- **Hygroscopicity**

  Several fast dissolving tablets are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence they need protection from humidity that calls for specialized product package.

- **Friability**

  In order to allow dispersible tablets to disintegrate rapidly in the mouth, they are made of either very porous or soft molded matrices or compressed into tablets with low compression force, which makes the tablet friable and/or brittle which are difficult to handle, often require specialized peel-off blister packing.

Mouth feel

Mouth feel is critical, and patients should receive a product that feels pleasant. Any large particles from the disintegrating tablet that are insoluble or slowly soluble in saliva would lead to an unpleasant gritty feeling. This can be overcome by keeping the majority of the particles below the detectable size limit. In some cases, certain flavors can imbibe an improved mouth feel perception, resulting in a product that is perceived as being less gritty, even if the only change is the flavor. Effervescence can be added to aid disintegration and improve mouth feel by reducing the "dryness" of a product.

SIGNIFICANCE[2]:

ODTs offer all advantages of solid dosage forms along with special advantages, include:

As ODTs are unit solid dosage forms, they provide good stability, accurate dosing, easy manufacturing, small packaging size, and easy to handle by patients.

Rapid disintegration of tablet results in quick dissolution and rapid absorption which provide rapid onset of action.

Medication as *bitter pill* has changed by excellent mouth feel property produced by use of flavors and sweeteners in ODTs.

Bioavailability of drugs that are absorbed from mouth, pharynx, and esophagus is increased.

Pre-gastric absorption of drugs avoids hepatic metabolism, which reduces the dose and increases the bio-availability.

Selection of ODT drug candidates[3]

Several factors must be considered when selecting drug candidates for delivery as ODT dosage forms. In general, an ODT is formulated as a bioequivalent line extension of an existing oral dosage form. Under these circumstances, it is assumed that the absorption of a drug molecule from the ODT occurs in the post gastric GIT segments, similar to the conventional oral dosage form.

It is possible that these differences may, in part, be attributed to the drug molecule, formulation, or a combination of both. If significantly higher plasma levels and systemic exposure have been observed, pregastric absorption leading to the avoidance of first-pass metabolism may play an important role. This situation may have implications for drug safety and efficacy, which may need to be addressed and assessed in a marketing application for an ODT (13). For example, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism and for drugs that have a substantial fraction of absorption in the oral cavity and segments of the pregastric GIT.

The ideal characteristics of a drug for dissolution in the mouth and pregastric absorption from an ODT include:

1. No bitter taste;
2. Dose lower than 20 mg;
3. Small to moderate molecular weight;
4. Good solubility in water and saliva;
5. Partially nonionized at the oral cavity's ph;
6. Ability to diffuse and partition into the epithelium of the upper git (log *p* >1, or preferably >2);
7. Ability to permeate oral mucosal tissue (15).
8. In contrast, the following characteristics may render a drug unsuitable for delivery as an odt:
9. Short half-life and frequent dosing;
10. Very bitter or otherwise unacceptable taste because taste masking cannot be achieved;
11. Require controlled or sustained release.
12. The drug dose must be lower than 400 mg for insoluble drugs and less than 60 mg for soluble drugs (because they dissolve quickly, odts cannot provide controlled or sustained release, except those that contain slow-dissolving, microparticulate-coated drugs, which quickly disperse and are swallowed.

Oral routes of drug absorption:

There are two permeation pathways for passive drug transport across the oral mucosa:

1. Paracelluloar and
2. Transcellular routes.

Descriptions of orally disintegrating dosage forms[3]:

Possible benefits of Orally disintegrating tablet drugs.

- **Clinical**
  1. Improved drug absorption
  2. Faster onset of action
  3. Minimized first-pass effect
  4. Improved Bioavailability

- **Medical**
  1. Better taste, no water needed
  2. Improved stability because of unit-dose packaging
  3. Manufactured with common process and conventional equipment

Orally disintegrating tablet manufacturers and technology characteristics:

Technology	In vitro Disintegration Times	Tablet hardness and Robustness	Packaging	Drug-loading dose(mg)	Marketed products worldwide
Advatab (Eurand)	15-30	Hard, robust	Bottles or blister pack	<700	2
DuraSolv (CIMA Labs)	<30	Hard, robust	Bottles or blister pack	<500	3
FlashDose (Biovail)	5-15	Soft, friable	Blister pack	<600	1
FlashTab (ethypharm SA)	30-60	Relatively durable	Blister pack	<650	3
Lyoc (Cephalon)	<10	Soft, friable	Blister pack	<1000	6
OraQuick (KVPharmaceuticals)	<20	Relatively durable	Bottles or blister pack	<500	1
OraSolv (CIMA Labs)	<30	Soft, fragile	Blister pack	<750	3
SATAB (Sato)	<10	Relatively durable	Blister pack	<600	7
WOWTAB (Yamanouchi)	<30	Relatively durable	Bottles or blister pack	<500	14
Zydis (Cardinal Health)	3-5	Very fragile	Blister pack	<400	15

Techniques used in the formulation of dispersible tablets

The performance of dispersible tablets depends on the technology used in their manufacture. The orally disintegrating property of the tablet is attributable to a quick ingress of water into the tablet matrix, which creates porous structure of the tablet matrix, which creates porous structure and results in rapid disintegration. Hence, the basic approaches to develop dispersible tablets include maximizing the porous structure of the tablet matrix, incorporating the appropriate disintegrating agent and using highly water-soluble excipients in the formulation.

Following technologies have been used by various researchers to prepare fast disintegrating tablets:

- Freeze-drying or lyophilization
- Tablet Molding
- Direct compression
- Wet granulation
- Spray drying
- Sublimation
- Taste masking
- Mass extrusion

Freeze-Drying or lyophilization

Freeze drying is the process in which water is subjected from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. Commonly used excipients with their uses and examples employed in formulation of dispersible tablets using Freeze-drying are listed below in the following table. A typical procedure involved in the formulation of dispersible tablets using this technique is mentioned here. The active drug was dissolved or dispersed in an aqueous solution of a carrier/polymer. The mixture dosed by weight and poured in the wells of the preformed blister packs. The trays holding the blister packs are passed through liquid nitrogen

freezing tunnel to freeze the drug solution or dispersion, and then the frozen blister packs are placed in refrigerated cabinets to continue the freeze-drying. After freeze-frying the aluminum foil backing is applied on a blister sealing machine. Finally the blisters are packaged and shipped.

Excipients and their uses in Freeze drying technique

Excipients	Use	Examples
Polymer	Strength and rigidity	Gelatin, alginate and dextrin
Polysaccharides	Crystallinity, hardness and palatability	Mannitol and sorbitol
Collapse protectants	Prevents shrinking	Glycerin
Flocculating agents	Uniform dispersion	Xanthan gum and acacia
Preservatives	Prevent microbial and fungal growth	Parabens
Permeation enhancer	Transmucosal permeability	Sodium lauryl sulphate
pH adjusters	Chemical stability	Citric acid and sodium hydroxide
Flavors and sweeteners	Patient compliance	-------
Water	Porous unit formation	-------

The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The Zydis formulation consist of a drug physically trapped in a water-soluble matrix (saccharine mixture and polymer), which is freeze dried to produce a product that dissolves rapidly when placed in mouth. The ideal candidate for Zydis

technology should be chemically stable and water insoluble and particle size preferably less than 59 mm. Water soluble drugs might form eutectic mixtures and not freeze adequately, so dose is limited to 60 mg and the maximum drug limit is 400 mg or water insoluble drug as large particle sizes might present sedimentation problems during manufacture. The major disadvantage of lyophilization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

Tablet Molding

The preparation of dispersible tablets using molding technology employs water-soluble ingredients so that the tablet dissolves completely and rapidly. The active ingredients in most cases are absorbed through the mucosal lining of the mouth. Molding process is of two types i.e., solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in molded plates to form a wetted mass (compression molding). The solvent then removed by air-drying. The tablets manufactured in this manner are less hastens dissolved. The heat molding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. Mannitol or Lactose) and pouring the suspension in the blister packing wells, solidifying the agar at room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of molded strength of the tablets, need to be incorporated. Taste masking is an added problem for this technology.

Direct compression

It is the convenient way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. This technique can now be applied to dispersible tablets because of the availability of improved tablet excipients, especially

1) Tablet disintegrants

2) Sugar-based excipients.

1) Addition of disintegrants: Addition of disintegrants in fast dissolving tablets, leads to quick disintegration of tablets and hence improves dissolution. In many fast dissolving tablet technologies based on direct compression, the disintegrants principally affect the rate of disintegration and hence the dissolution. The introduction so-called superdisintegrants and a better understanding of their properties have increased the popularity of this technology. Tablet disintegration time can be optimized by concentrating the disintegrants. Below critical concentration, tablet disintegration time is inversely proportional to disintegrants concentration. Above the critical concentration level, however, disintegration time remains approximately constant or even increases.

Microcrystalline cellulose, cross linked carboxymethyl cellulose sodium, cross linked polyvinyl pyrrolidone and partially substituted hydroxypropyl cellulose, though water insoluble, absorb water and swell due to capillary action and are considered as effective disintegrants in the preparation of dispersible tablets.

Fast disintegration of tablets can also be achieved by incorporating effervescent disintegrating agents, which generates carbon dioxide. This phenomenon also resulted in partial taste masking of unacceptable taste of the drug. The major drawback of effervescent excipients is their hygroscopicity (i.e., the ability to absorb atmospheric moisture). Hence, their manufacture requires control of humidity conditions and protection of the final product. This is reflected by the overall cost of the product.

2) Sugar-based excipients: The alternative approach for the development of dispersible tablets by direct compression is the use of sugar-based excipients (e.g. dextrose, fructose, isomalt, maltose, mannitol, sorbitol, starch hydrolyse, polydextrose, and xylitol), which display high aqueous solubility and sweetness, and hence, impart taste masking and a pleasing mouth feel.

Wet granulation

The concept of wet granulation is well-known and conventional process for tablet formation, used to reduced bitterness of active drug with water insoluble materials. In a wet granulation, the material to be granulated, usually in powder forms, is wetted with an

aqueous composition of a granulating agent to cause the powdered material to agglomerates. This agglomerated product is subsequently dried and then milled to reduced size in suitable form.

Wet granulation is often carried out utilizing a high-shear mixer. The high-shear granulation process is a rapid process which is susceptible for over-wetting. Thus, the liquid amount added is critical and the optimal amount is affected by the properties of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to monitor the rheological properties of the wet mass during agglomeration and, thereby, have been used to determine the end-point of water addition. However, these methods are affected by the equipment variables. Hence, additional process monitoring techniques would be valuable.

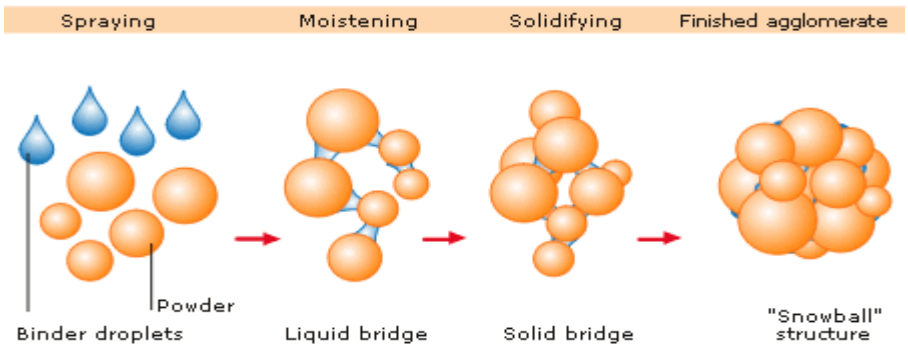


Figure 1: Process principle for formation of agglomerates

Wet granulation is often carried out utilizing a high-shear mixer. The high-shear granulation process is a rapid process which is susceptible for over-wetting. Thus, the liquid amount added is critical and the optimal amount is affected by the properties of the raw materials. Power consumption of the impeller motor and the impeller torque have been applied to monitor the rheological properties of the wet mass during agglomeration and, thereby, have been used to determine the end-point of water addition. However, these methods are affected by the equipment variables. Hence, additional process monitoring techniques would be valuable.

Important steps involved in wet granulation

- Mixing of drug(s) and excipients.
- Preparation of binder solution.
- Mixing of binder solution with powder mixture to form wet mass.
- Coarse screening of wet mass using a suitable sieve (6-12 screens).
- Drying of moist granules.
- Screening of dry granules through a suitable sieve (14-20 screens).
- Mixing of screened granules with disintegrant, glidant, and lubricant.

Limitations of wet granulation

- The greatest disadvantage of wet granulation is its cost. It is an expensive process because of labor, time, equipment, energy and space requirements.
- Loss of material during various stages of processing.
- Stability may be a major concern for moisture sensitive or thermo labile drugs.
- Multiple processing steps give complexity and make validation and control difficult.
- An inherent limitation of wet granulation is that any incompatibility between formulation components is aggravated.

Spray drying

Spray drying is used in pharmaceutical industries to produce highly porous powders. The processing solvent is evaporated rapidly by spray drying, which renders the product highly porous and thus can be used in manufacturing dispersible tablets. In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate or croscarmellose sodium or crospovidone are used as superdisintegrants. Tablets manufactured from the spray dried powder have been reported to disintegrate in less than 20 sec in aqueous medium.

Sublimation

The key to rapid disintegration for dispersible tablets is the presence of a porous structure in the tablet matrix. Conventional compressed tablets that contain highly water-soluble ingredients often fall to dissolve rapidly because of low porosity of the matrix.

Hence, to generate porous matrix, volatile ingredients are used that are later subjected to a process of sublimation. e.g. ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, hexamethonium tetramine, naphthalene, phthalic anhydride, urea, and urethane were compressed along with other excipients into a table. The volatile material was then removed by sublimation, leaving behind a porous matrix. Solvents such as cyclohexane and benzene were also suggested for the generation of porosity in the matrix.

Taste masking

Taste masking is an essential requirement for fast dissolving tablets for commercial success. Taste masking of the active ingredients can be achieved by various techniques. Drugs with unacceptable bitter taste can be microencapsulated into pH sensitive acrylic polymers. Cefuroxime axetil is microencapsulated in various types of acrylic polymers (e.g. Eudragit E, Eudragit L-55 and Eudragit RL) by solvent evaporation and solvent extraction techniques. These polymer microspheres showed efficient taste masking and complete dissolution in a short period. Fine granules of drug and disintegrant (e.g. low substituted hydroxypropyl cellulose) when coated with a water insoluble polymer (e.g. ethylcellulose) masked the bitter taste of sparfloxacin. The addition of low substituted hydroxypropyl cellulose as disintegrant to the drug in cores resulted in increased dissolution rate and bioavailability of sparfloxacin compared to its conventional tablets.

Mass extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

Role of Superdisintegrants in the manufacturing of dispersible tablets

Disintegrating agents are substances routinely included in tablet formulations and in some hard shell capsule formulations to promote moisture penetration and dispersion of the matrix of the dosage form in dissolution fluids. An oral solid dosage form should ideally disperse into the primary particles from which it was prepared. Although various compounds have been proposed and evaluated as disintegrants, relatively few are in common usage today. Traditionally, starch has been the disintegrant of choice in tablet formulations, and it is still widely used. For instance, starch generally has to be present at levels greater than 5 % to adversely affect compactibility, especially in direct compression. Moreover, intragranular starch in wet granulations is not as effective as dry starch.

Mechanism of Superdisintegrants

There are four major mechanisms for tablets disintegration as follows

- **Swelling**

  Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling. Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

- **Porosity and capillary action (Wicking)**

  Disintegration by capillary action is always the first step. When we put the tablet into suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug/excipient and on tableting conditions. For these types of disintegrants maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary which helps in disintegration by creating a hydrophilic network around the drug particles.

- **Due to disintegrating particle/particle repulsive forces**

  Another mechanism of disintegration attempts to explain the swelling of tablet made with 'nonswellable' disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

- **Due to deformation**

  During tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a breakup of the tablet.

Method of Addition of Disintegrants

The ideal disintegrant should have the following characteristics:

- Poor solubility
- Poor gel formation
- Good hydration capacity
- Good molding and flow properties
- No tendency to form complexes with the drugs

Disintegrants are essentially added to tablet granulation for causing the compressed tablet to break or disintegrate when placed in aqueous environment. There are two methods of incorporating disintegrating agents into the tablet:

- Internal Addition (Intragranular)
- External Addition (Extragranular)
- Partly Internal and External

In external addition method, the disintegrant is added to the sized granulation with mixing prior to compression. In Internal addition method, the disintegrant is mixed with other powders before wetting the powder mixtures with the granulating fluid. Thus the disintegrant is incorporated within the granules. When these methods are used, part of disintegrant can be added internally and part externally. This provides immediate disruption of the tablet into previously compressed granules while the disintegrating agent within the granules produces further erosion of the granules to the original powder particles. The two step method usually produces better and more complete disintegration than the usual method of adding the disintegrant to the granulation surface only.

Factors affecting action of disintegrants

- Percentage of disintegrants present in the tablets.
- Types of substances present in the tablets.
- Combination of disintegrants.
- Presence of surfactants.
- Hardness of the tablets.
- Nature of Drug substances.
- Mixing and Screening.

Because of the increased demands for improved dissolution requirements, there are currently, a new generation of "**Superdisintegrants**". These newer substances are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength. On contact with water the **superdisintegrants** swell, hydrate, change volume or form and produce a disruptive change in the tablet. Effective **superdisintegrants** provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulations containing high-dose drugs. They are widely used in wet granulation and direct compression applications.

Classification of superdisintegrants

Structural type (NF name)	Description	Trade name (manufacturer)
Modified starches (Sodium starch glycolate, NF)	Sodium carboxymethyl starch; the carboxymethyl groups induces hydrophilicity and cross-linking reduces solubility.	Explotab®(Edward Mendell Co.), Primojel® (Generichem Corp.), Tablo® (Blanver, Brazil)
Modified cellulose (Croscarmellose, NF)	Sodium carboxymethyl cellulose which has been cross-linked to render the material insoluble.	AcDiSol® (FMC Corp.), Nymcel ZSX® (Nyma, Netherlands), Primellose® (Avebe, Netherlands) Solutab® (Blanver, Brazil)
Cross-linked poly-vinylpyrrolidone (Crospovidone, NF)	Cross-linked polyvinylpyrrolidone; the high molecular weight and cross-linking render the material insoluble in water.	Crospovidone M® (BASF Corp.), Kollidon CL® (BASF Corp.), Polyplasdone XL (ISP Corp.)

Three major groups of compounds have been developed which swell to many times their original size when placed in water while producing minimal viscosity effects.[19]

1. Modified starches - Sodium Carboxymethyl Starch (Chemically treated Potato Starch) i.e. Sodium Starch Glycolate (Explotab, Primogel)

Mechanism of Action: Rapid and extensive swelling with minimal gelling.

Effective Concentration: 4-6 %. Above 8 %, disintegration times may actually increase due to gelling and its subsequent viscosity producing effects.

2.Cross-linked polyvinylpyrrolidone - water insoluble and strongly hydrophilic. i.e. Crospovidone (Polyplasdone XL, Kollidon CL)

Mechanism of Action: Water wicking, swelling and possibly some deformation recovery.

Effective Concentration: 2-4 %

3.Modified cellulose- Internally cross-linked form of Sodium carboxymethyl cellulose. i.e. Ac-Di-Sol (Accelerates Dissolution), Nymcel

Mechanism of Action: Wicking due to fibrous structure, swelling with minimal gelling.

Effective Concentration: 1-3 % (Direct Compression), 2-4 % (Wet Granulation).

Advantages

- Effective in lower concentrations than starch.
- Less effect on compressibility and flow ability.
- More effective intragranularly.

Disadvantages

- More hygroscopic (may be a problem with moisture sensitive drugs).
- Some are anionic and may cause some slight *in vitro* binding with cationic drugs (not a problem *in vivo*).

Packaging of dispersible tablets

Some of the dispersible tablets are stable during storage, e.g. for 2 years or even 3 years in conventional packaging and these type of dosage forms are stored in HDPE bottles, blister and strip packs.

Some of the examples of dispersible tablets

- Aspirin dispersible tablet
- Cefadroxil dispersible tablet
- Fast dispersible Ibuprofen tablet
- Piroxicam dispersible tablet

- Cefpodoxime Proxetil dispersible tablet
- Cefixime *dispersible Tablet*
- Rifampicin and Isoniazid dispersible tablets

LITERATURE REVIEW

- ***By Suresh Bandari et al. (2008)*** [2] Review article: Oral drug delivery remains the preferred route for administration of various drugs. Recent developments in the technology have prompted scientists to develop orally disintegrating tablets (ODTs) with improved patient compliance and convenience. ODTs are solid unit dosage forms which disintegrate or dissolve rapidly in the mouth without chewing and water. It describes the various formulation aspects, disintegrants employed and technologies developed for ODTs, along with various excipients, evaluation tests, marketed formulations, and drugs explored in this field.

- ***C.Mallikarjuna setty et al. (Apr 2008)*** [15] Development of fast dispersible *aceclofenac* tablets: effect of functionally of super disintegrants. Disintegration time and dissolution parameters decreased with increase in the level of croscarmellose sodium.

- ***D M Patel et al. (Feb 2008)*** [14] The purpose of thes investigation was to develop fast dissolving tablets of Etoricoxib. Granules containing Etoricoxib, menthol, crospovidone, aspartame and mannitol were prepared by wet granulation technique. Menthol was sublimed from the granules by exposing the granules to vaccum. The porous granules were then compressed in to tablets. The tablets were evaluated for percentage friability and disintegration time. Optimization of fast dissolving *Etoricoxib* tablets prepared by sublimation technique. The dissolving tablets with improved *etoricoxib* dissolution could be prepared by sublimation of tablet containing suitable subliming agent.

- ***Shailesh shatma et al. (Jan 2008)*** [11] Fast dissolving tablets (FDT) *promethazine theoclate* were prepared by direct compression method after incorporating superdisintegrants Ac-Di-Sol, SSG and Crospovidone in

different concentrations. Formulation and characterization of fast-dissolving tablets of *promethazine theoclate* with USP type-II apparatus.

- ***S.Jacob et al. (Oct 2007)*** [13] Novel co-processed excipients of mannitol and microcrystalline cellulose for preparing fast dissolving tablets of *glipizide* Using spray dring technique. Improves the fast dissolving tablet could be prepared by the co-processed mixture of microcrystalline cellulose and mannitol.

- ***Sheetal malke et al. (Apr 2007)*** [12] Formulation and evaluation of *oxcarbazepine* fast dissolving tablets. It prepared with Avicel 102 as diluent & Ac-Di-Sol as a superdisintegrants by wet granulation process. All the formulations were evaluated for characteristics such as Hardness, Friability, Weight variation, Wetting ability, Disintegration time and Dissolution rate. A modified disintegration method was used for studying disintegration. Since the drug is poorly water soluble, drug release was tested in various media and effect of surfactant on drug release was studied.

- ***Jack Y. Zheng et al***[23] developed the purpose of this study is to assess the feasibility for taste masking and comparison of taste intensity during formulation development using a multichannel taste sensor system (e-Tongue). Taste-masking efficiency was evaluated using quinine as a bitter model compound and a sweetener, acesulfame K, as a bitterness inhibitor. the bitterness inhibition of quinine by using other known taste-masking excipients including sodium acetate, NaCl, Prosweet® flavor, and Debittering® powder or soft drinks could be detected by the e-Tongue. These results further suggest that the e-Tongue should be useful in a taste-masking evaluation study on selecting appropriate taste-masking excipients for a solution formulation or a reconstitution vehicle for a drug-in-bottle formulation. Based on the group distance, the relative intensity of bitterness for these compounds could be ranked in the following order: ranitidine

HCl > prednisoloneNa > quinine HCl ∿ phenylthiourea > paracetamol ≫ sucrose octaacetate > caffeine. In conclusion, the multichannel taste sensor or e-Tongue may be a useful tool to evaluate taste-masking efficiency for solution formulations and to compare bitterness intensity of formulations and drug substances during pharmaceutical product development.

- ***Omaima A. Sammour et.al (2006)***[16] investigate the increase in the solubility and dissolution rate of Rofecoxib by the preparation of its solid dispersion with PVP K -30(1:9) using Solvent evaporation method. In an attempt to construct a statistical model for the prediction of disintegration time and percentage friability 3^2 randomized full and reduced factorial design was used. The obtained results showed that dispersion of the drug in the polymer considerably enhanced the dissolution rate.

- ***Mishra D.N. et.al.(2005)***[17] Carried out formulation of rapidly disintegrating tablets of meloxicam using super disintegrates like sodium starch glycolate, Ac-di-sol and Low molecular weight HPMC. The disintegration time in the oral cavity was tested And was found to be around 1 minute. It was concluded that rapidly disintegrating tablets with proper hardness rapidly disintegrates in the oral cavity with enhanced Dissolution rate.

- ***Sheftell FD et.al (2005)***[18] developed fast disintegrating / Rapid – release Formulation of Sumatriptan to enhance tablet disintegration and drug dispersion and potentially, improve absorption. Two studies were conducted comparing the time to onset of relief from moderate or severe migraine pain with the fast disintegrating / Rapid Release Formulation of Sumatriptan tablets 50 and 100 mg and placebo. Using a personal digital assistant, patients recorded the time of dosing and the at which pain severity reached none that or mild in real time so that the time to onset of relief could be measured as a continuous variable. Results shown that Sumatriptan tablets in a fast disintegrating / Rapid release formulation were effective for the acute

treatment of moderate to severe migraine pain, were generally well tolerated and achieved an onset of pain relief as early as 20 min. for - 100 mg and as early as 30 min.for 50 mg.

- ***Mukesh G. et.al. (2004)***[19] Formulates mouth dissolving tablet of Nimesulide. Granules containing Nimesulide, camphor, crospovidone and lactose were prepared by wet Direct Compression technique. Camphor was sublimed from the dried granules by exposure by vacuum. The porous granules were then compressed and evaluated. The result for obtaining a rapidly disintegrating **dosage** forms, tablets should be prepared using an optimum concentration of camphor and a higher percentage of crospovidone.

- ***Yourong Fu et.al (2004)***[20] conducted comprehensive review of current technologies in making fast dissolving tablet. Mannose was chosen as the best candidate for the investigation. The mechanisms of fast dissolution of mannose tablets were studied. The strength of mannose tablets was improved by the moisture treatment process. Poly (acrylic acid), super porous hydrogel (SPH) particles showed a high swelling property in various aqueous solutions and had a very good compressibility and compatibility. The effect of SPH particles on disintegration time and hardness of fast dissolving tablet were compared to common super disintegrates such as sodium starch glycolate and carboxymethyl cellulose sodium. The addition of SPH significantly decreased the disintegration time of FDT.S but had a negative impact on tensile strength. The results indicates PAA SPH is a promising super – disintegrates for making FDT'S.

- ***Mishra et al***[21] assessed the suitability of spray dried excipient base in the formulation of oral disintegrating tablets of valdecoxib and metoclopramide. Superdisintegrants (such as Ac-Di-Sol, Kollidon CL, sodium starch glycolate), diluent (mannitol) along with sweetening agent (aspartame) were used in the formulation of tablets. Using the same excipients, the tablets were

prepared by direct compression and were evaluated in the similar way. Maximum drug release and minimum disintegrating time were observed with Kollidon CL excipient base as compared to tablets prepared by direct compression, showing the superiority of the spray dried excipient base technique over direct compression technique

- ***Moen and Keating et al***[22] developed a new fast-disintegrating sumatriptan tablet with the goal of speeding absorption and onset of effect compared with standard sumatriptan tablets. Compared with placebo, pain relief was significantly greater with sumatriptan fast disintegrating tablets 100mg at 25 and 17 minutes following administration and with sumatriptan fast disintegrating tablets 50mg at 50 and 30 minutes following administration, to severe migraine.

AIM AND OBJECTIVE

The aim is to develop and formulate PREDNISOLONE SODIUM PHOSPHATE Orally Disintegrating tablets using different concentrations of taste masking and enteric coating materials comparable to the innovator product with better stability,high product feasibility,and excellent patient compatability.

The Objective of present study is to mask the bitter taste of the API and prepare a Orally disintegrating tablets using taste masking materials, enteric coating materials and super disintegrants which is pharmaceutically equivalent to the Innovator product.

PLAN OF WORK

- To carry out a brief literature review.
- To do Pre-formulation studies:

  1) API- Tap density, bulk density, angle of repose and compressibility index.

  2) BLEND- Tap density, bulk density, angle of repose and compressibility index.
- To Formulate of ***PREDISOLONE Sodium Phosphate*** *Orally Disintegrated Tablets*.
- To Evaluate ***PREDISOLONE Sodium Phosphate*** *Orally Disintegrated Tablets* for Disintegration time and Dissolution study.
- Selection of best formulation on the basis of Disintegration time and In-vitro drug release.
- To compare the best formulation with that of the innovator.

MATERIALS AND METHODS

INSTRUMENT LIST.

Instruments	Supplier/Manufacturer
Compression machine	Rimek minipress
Hot air oven	Eltek motors, Mumbai
RMG mixer	Sreenex machines pvt. Limited, Hyderabad
Sieves	Jayanth test sieves. Mumbai.
Balances	Citizen scale pvt. Limited, Thane.
Density tester	Electrolab ,Mumbai
Disintegration apparatus	Electrolab, Mumbai
Dissolution apparatus	Electrolab, Mumbai
HPLC	Waters India pvt. limited,
Hardness tester	Dr.Schleuniger pharmatron,U S A.
Friabilator	Electrolab, Mumbai
Helium lamp (LOD)	Metteler- Toledo

MATERIALS LIST.

Materials	Supplier/Manufacturer
Prednisolone sodium phosphate	IPCA Laboratories
Avicel PH101	FMC Polymers
Poly ethylene Glycol 4000	BASF Corporation
Ethyl cellulose 4CPS	The DOW chemical company
Mannitol spray dried	SPI polyol, 321, new castle.
Eudragit EPO	M/s. DEGUSSA
Eudragit L100	M/s. DEGUSSA
Crospovidone XL-10	M/s. ISP Technologies
Ethyl cellulose	The DOW chemical company
Aspartame	Neutrasweet pharma agencies
Sodium Bicarbonate	Merk Chemicals
Citric acid	Merk Chemicals
Aerosil	M/s. DEGUSSA
Mint flavors	Pan aroma, Chennai

METHODS

Innovator Product details:

Innovator product details including their manufacturer name, description, physical parameters and dissolution profile were given in the following table

Innovator Product details:

Name of the product	ORAPRED – 30mg
Manufacturer name	Alliant Pharmaceuticals Alpharetta, GA 30022,USA.
Color	White
Description	white, flat faced, beveled tablets, debossed with ORA on one side and 30 on the other.
Package	They are supplied as 48 tablets per carton. Each carton has 8 cards containing 6 tablets.

Physical parameters of Innovator product:

Parameters	**30mg**
Weight of the tablet (mg)	605
Thickness (mm)	5.14
Hardness (kp)	3.08
Disintegration time (sec)	26
Dispersion time (sec)	60

PREFORMULATION STUDIES[6]:

Drug-excipient compatibility studies:

- The proper design and the formulation of a dosage form require consideration of the physical, chemical and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe.

- The compatibility studies provide the framework for the drugs combination with excipients in the fabrication of the dosage form. The study was carried out to establish that the therapeutically active drug has not undergone any changes, after it has been subjected to processing steps during formulation of tablets.

- Compatibility studies were carried out by mixing definite proportions of drug and excipient and kept in glass vials, which are stored at 55°C (2 weeks) and 40±2°C/75±5 % RH(4 weeks).

Physical parameters of blend:

The following evaluation parameters studies were performed for the Prednisolone sodium Phosphate.

Sieve Analysis:

Pass a define mass of the sample through various sieves and calculate the percentage of retained powder and fines passed through sieves.

$$\text{Percentage of powder retained} = \frac{\text{Weight of the powder}}{\text{Total weight of the powder}} \times 100$$

Bulk density:

It is the ratio between a given mass of powder and its bulk volume.

$$\text{Bulk density} = \frac{\text{Mass of powder}}{\text{Total weight of the powder}}$$

A given quantity of the powder is transferred to the measuring cylinder and it is tapped mechanically either manually or mechanical device till a constant volume is obtained. This volume is bulk volume (v) and it includes the true volume of the powder and void space among the powder particles.

Angle of repose:

Angle of repose is defined as the maximum angle possible between the surface of pile of powder and the horizontal plane. The granule mass should allowed to flow out of the funnel orifice on a plane paper kept on the horizontal surface. This forms a pile of granules on the paper.

$$\textbf{Tan } \theta = h/r \qquad \theta = \tan^{-1}(h/r)$$

Where, h= height of the pile

r= radius of the pile

Tapped density:

Tapped density is defined as the ratio between weight of the sample powder taken and the tapped volume.

$$\text{Tapped density}(\rho t) = M/V_f$$

Where , M = weight of sample powder taken

V_f = tapped volume

Compressibility index /Carr's index:

Based on the apparent bulk density and the tapped density, the percentage compressibility index of the powder was determined by using the following formula.

$$\text{Compressibility index} = \frac{\text{Tapped density-Bulk density}}{\text{Tapped density}} \times 100$$

Hausner ratio:

By calculating tapped density and bulk density, the Hausner ratio can be calculated.

Hausner ratio = ρ_t / ρ_o

Where, ρ_t = tapped density

ρ_o = bulk density

Flow Properties of Powder.

S. No	Angle of repose	Carr's index	Hausner's ratio	Properties
1	25-30	5-12	1.00-1.11	Free Flowing
2	30-35	12-16	1.12-1.18	Good
3	35-40	18-21	1.19-1.25	Fair
4	40-55	23-35	1.35-1.45	Poor
5	55-65	33-38	1.46-1.59	Very poor
6	>65	>40	>1.60	Extremely poor

There are various in-process control parameters should be performed. They are

During tablet compression:

- Appearance
- Average weight
- Weight uniformity
- Hardness

- Thickness
- Disintegration time
- Dissolution[8]

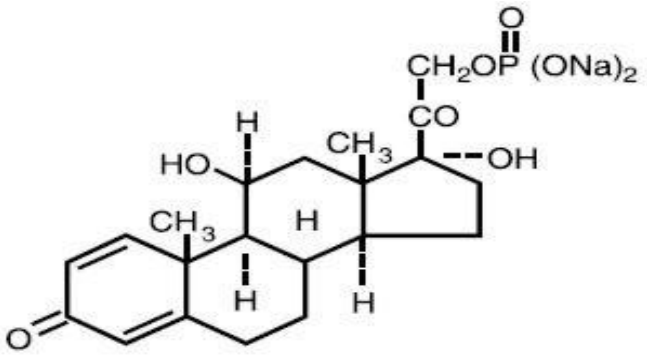
Method development:

Formulation of *Prednisolone* orally disintegrating tablets by method of taste masking with PEG 4000, Ethyl cellulose, Eudragit EPO and Eudragit L100. Tablets can be formulated by wet granulation method.

DRUG PROFILE

PREDNISOLONE SODIUM PHOSHATE

Chemical name: pregna-1, 4-diene-3,20-dione,11, 17-dihydroxy-21-(phosphonooxy), disodium salt(11ß)-



The empirical formula: $C_{21}H_{27}Na_2O_8P$;

The molecular weight: 484.39

Physical properties

Color: White or slightly yellowish

State/form: Friable granules or powder

Solubility: It is freely soluble in water; soluble in methanol; slightly soluble in alcohol and in chloroform; and very slightly soluble in acetone and in dioxane.

Pharmacokinetics:

Absorption: Absorbed from GIT

Bioavailability: Found to be about 62%. The fraction of the dose recovered in the urine as the hydroxylated metabolites of prednisone and prednisolone was lower after the oral prednisone dose, suggesting that poor absorption of prednisone was the main cause of the low bioavailability.

Plasma binding: 70-90%

Elimination: Eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates.

Dose: Available in strengths containing 13.4 mg, 20.2 mg, and 40.3 mg prednisolone sodium phosphate (equivalent to 10 mg, 15 mg, or 30 mg prednisolone base, respectively).

Pharmacodynamics:

Pharmacological Category: Glucocorticoid

Clinical Pharmacology[4]:

Naturally occurring glucocorticoids (hydrocortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems.

Prednisolone is a synthetic adrenocortical steroid drug with predominantly glucocorticoid properties. Some of these properties reproduce the physiological actions of endogenous glucocorticosteroids, but others do not necessarily reflect any of the adrenal hormones normal functions; they are seen only after administration of large therapeutic doses of the drug. The pharmacological effects of prednisolone which are due to its glucocorticoid properties include: promotion of gluconeogenesis; increased deposition of glycogen in the liver; inhibition of the utilization of glucose; anti-insulin activity; increased catabolism of protein; increased lipolysis; stimulation of fat synthesis and storage; increased glomerular filtration rate and resulting increase in urinary excretion of urate (creatinine excretion remains unchanged); and increased calcium excretion.

Depressed production of eosinophils and lymphocytes occurs, but erythropoiesis and production of polymorphonuclear leukocytes are stimulated. Inflammatory processes (edema, fibrin deposition, capillary dilatation, migration of leukocytes and phagocytosis) and the later stages of wound healing (capillary proliferation, deposition of collagen, cicatrization) are inhibited.

Prednisolone can stimulate secretion of various components of gastric juice. Suppression of the production of corticotropin may lead to suppression of endogenous corticosteroids. Prednisolone has slight mineralocorticoid activity, whereby entry of sodium into cells and loss of intracellular potassium is stimulated. This is particularly evident in the kidney, where rapid ion exchange leads to sodium retention and hypertension.

Prednisolone is rapidly and well absorbed from the gastrointestinal tract following oral administration. Prednisolone is 70-90% protein-bound in the plasma and it is eliminated from the plasma with a half-life of 2 to 4 hours. It is metabolized mainly in the liver and excreted in the urine as sulfate and glucuronide conjugates.

The systemic availability, metabolism and elimination of prednisolone after administration of single weight-based doses (0.8 mg/kg) of intravenous (IV) prednisolone and oral prednisone were reported in a small study of 19 young (23 to 34 years) and 12 elderly (65 to 89 years) subjects. Results showed that the systemic availability of total and unbound prednisolone, as well as interconversion between prednisolone and prednisone were independent of age. The mean unbound fraction of prednisolone was higher, and the steady-state volume of distribution (Vss) of unbound prednisolone was reduced in elderly patients. Plasma prednisolone concentrations were higher in elderly subjects, and the higher AUCs of total and unbound prednisolone were most likely reflective of an impaired metabolic clearance, evidenced by reduced fractional urinary clearance of 6b-hydroxyprednisolone. Despite these findings of higher total and unbound prednisolone concentrations, elderly subjects had higher AUCs of cortisol, suggesting that the elderly population is less sensitive to suppression of endogenous cortisol or their capacity for hepatic inactivation of cortisol is diminished.

Oral administration of single doses of 30 mg prednisolone base equivalent of Orapred ODT and Pediapred Solution to 21 adult volunteers yielded comparable pharmacokinetic data:

Dose* (30 mg prednisolone base equivalent)	AUC_{0-} (nghr/mL) (S.D.)	C_{max} (nghr/mL)** (S.D.)
Pediapred Solution	2426.1 (360.0)	461.33 (77.94)
Orapred ODT	2408.1 (361.5)	420.91 (78.28)

*Administered under fasting conditions.

**Mean values of 21 normal volunteers.

USES: It is used for treatment of severe inflammatory conditions including allergies, arthritis, asthma, or skin reactions. It may also be used to treat certain blood, adrenal gland, eye, respiratory, or bowel conditions. It may also be used for other conditions as determined by your doctor. Orapred ODT is a corticosteroid. It works by modifying the body's immune response to various conditions and decreasing inflammation.

HOW TO USE: This medication is dissolved in the mouth on top of the tongue. It may also be swallowed whole with water.

Side Effects:

(Listed alphabetically under each subsection):

Cardiovascular: Hypertrophic cardiomyopathy in premature infants.

Dermatologic: Facial erythema; increased sweating; impaired wound healing; may suppress reactions to skin tests; petechiae and ecchymoses; thin fragile skin; urticaria; edema.

Endocrine: Decreased carbohydrate tolerance; development of cushingoid state; hirsutism; increased requirements for insulin or oral hypoglycemic agents in diabetic patients; manifestations of latent diabetes mellitus; menstrual irregularities; secondary adrenocortical and pituitary unresponsiveness, particularly in times of stress, as in trauma, surgery or illness; suppression of growth in children.

Fluid and Electrolyte Disturbances: Congestive heart failure in susceptible patients; fluid retention; hypertension; hypokalemic alkalosis; potassium loss; sodium retention.

Gastrointestinal: Abdominal distention; elevation in serum liver enzyme levels (usually reversible upon discontinuation); pancreatitis; peptic ulcer with possible perforation and hemorrhage; ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads; loss of muscle mass; muscle weakness; osteoporosis; pathologic fracture of long bones; steroid myopathy; tendon rupture; vertebral compression fractures.

Neurological: Convulsions; headache; increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment; psychic disorders; vertigo.

Ophthalmic: Exophthalmos; glaucoma; increased intraocular pressure; posterior subcapsular cataracts.

Contraindications:

Systemic fungal infections, hypersensitivity to the drug or any of its components

Drug Interactions:

Drugs such as barbiturates, phenytoin, ephedrine, and rifampin, which induce hepatic microsomal drug metabolizing enzyme activity may enhance metabolism of prednisolone and require that the dosage of Orapred be increased.

Increased activity of both cyclosporin and corticosteroids may occur when the two are used concurrently. Convulsions have been reported with this concurrent use.

Estrogens may decrease the hepatic metabolism of certain corticosteroids thereby increasing their effect.

Ketoconazole has been reported to decrease the metabolism of certain corticosteroids by up to 60% leading to an increased risk of corticosteroid side effects.

Co administration of corticosteroids and warfarin usually results in inhibition of response to warfarin, although there have been some conflicting reports. Therefore, coagulation indices should be monitored frequently to maintain the desired anticoagulant effect.

Concomitant use of aspirin (or other non-steroidal anti-inflammatory agents) and corticosteroids increases the risk of gastrointestinal side effects. Aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. The clearance of salicylates may be increased with concurrent use of corticosteroids.

When corticosteroids are administered concomitantly with potassium-depleting agents (i.e., diuretics, amphotericin-B), patients should be observed closely for development of hypokalemia. Patients on digitalis glycosides may be at increased risk of arrhythmias due to hypokalemia.

Concomitant use of anticholinesterase agents and corticosteroids may produce severe weakness in patients with myasthenia gravis. If possible, anticholinesterase agents should be withdrawn at least 24 hours before initiating corticosteroid therapy.

Due to inhibition of antibody response, patients on prolonged corticosteroid therapy may exhibit a diminished response to toxoids and live or inactivated vaccines. Corticosteroids may also potentiate the replication of some organisms contained in live attenuated vaccines. If possible, routine administration of vaccines or toxoids should be deferred until corticosteroid therapy is discontinued.

Because corticosteroids may increase blood glucose concentrations, dosage adjustments of antidiabetic agents may be required.
Corticosteroids may suppress reactions to skin tests.

STORAGE: Store at room temperature between 68-77 degrees F (20-25 degrees C) away from light and moisture. Keep all medicines away from children and pets.

LIST OF EXCIPIENTS USED

POLYETHYLENE GLYCOL

Nonproprietary Names:

BP: Macrogol 400

JP : Macrogol 400
Macrogol 1500
Macrogol 4000
Macrogol 6000
Macrogol 20000

PhEur: Macrogola

USPNF: Polyethylene glycol

Synonyms: Carbowax; Carbowax Sentry; Lipoxol; Lutrol E; PEG; Pluriol E; polyoxyethylene glycol.

Chemical Name and CAS Registry Number: α-Hydro-ω-hydroxypoly (oxy-1, 2-ethanediyl) [25322-68-3]

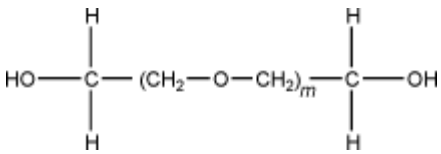
Empirical Formula and Molecular Weight: $HOCH_2(CH_2OCH_2)_mCH_2OH$ where m represents the average number of oxyethylene groups. Alternatively, the general formula $H(OCH_2CH_2)_nOH$ may be used to represent polyethylene glycol, where n is a number m in the previous formula + 1.

Structural formula and molecular weight of typical polyethylene glycol polymers:

Grade	*m*	Average molecular weight
PEG 200	4.2	190–210
PEG 300	6.4	285–315

Grade	*m*	Average molecular weight
PEG 400	8.7	380–420
PEG 540 (blend)	—	500–600
PEG 600	13.2	570–613
PEG 900	15.3	855–900
PEG 1000	22.3	950–1 050
PEG 1450	32.5	1 300–1 600
PEG 1540	28.0–36.0	1 300–1 600
PEG 2000	40.0–50.0	1 800–2 200
PEG 3000	60.0–75.0	2 700–3 300
PEG 3350	75.7	3 000–3 700
PEG 4000	69.0–84.0	3 000–4 800
PEG 4600	104.1	4 400–4 800
PEG 8000	181.4	7 000–9 000

Structural Formula:



Functional Category:

Ointment base; plasticizer; solvent; suppository base; tablet and capsule lubricant

Applications in Pharmaceutical Formulation or Technology:

Polyethylene glycols (PEGs) are widely used in a variety of pharmaceutical formulations including parenteral, topical, ophthalmic, oral, and rectal preparations. It has been used experimentally in biodegradable polymeric matrices used in controlled-release systems.

In solid-dosage formulations, higher-molecular-weight polyethylene glycols can enhance the effectiveness of tablet binders and impart plasticity to granules. However, they have only limited binding action when used alone, and can prolong disintegration if present in concentrations greater than 5% w/w. When used for thermoplastic granulations, a mixture of the powdered constituents with 10–15% w/w PEG 6000 is heated to 70–75°C. The mass becomes paste like and forms granules if stirred while cooling. This technique is useful for the preparation of dosage forms such as lozenges when prolonged disintegration is required.

In film coatings, solid grades of polyethylene glycol can be used alone for the film-coating of tablets or can be useful as hydrophilic polishing materials. Solid grades are also widely used as plasticizers in conjunction with film-forming polymers. Polyethylene glycols are useful as plasticizers in microencapsulated products to avoid rupture of the coating film when the microcapsules are compressed into tablets.

Description:

The USPNF 23 describes polyethylene glycol as being an addition polymer of ethylene oxide and water. Polyethylene glycol grades 200–600 are liquids; grades 1000 and above are solids at ambient temperatures.

Liquid grades (PEG 200–600) occur as clear, colorless or slightly yellow-colored, viscous liquids. They have a slight but characteristic odor and a bitter, slightly burning taste. PEG 600 can occur as a solid at ambient temperatures.

Solid grades (PEG>1000) are white or off-white in color, and range in consistency from pastes to waxy flakes. They have a faint, sweet odor. Grades of PEG 6000 and above are available as free-flowing milled powders.

Solubility:

All grades of polyethylene glycol are soluble in water and miscible in all proportions with other polyethylene glycols (after melting, if necessary). Aqueous solutions of higher-molecular-weight grades may form gels.

Liquid polyethylene glycols are soluble in acetone, alcohols, benzene, glycerin, and glycols. Solid polyethylene glycols are soluble in acetone, dichloromethane, ethanol (95%), and methanol; they are slightly soluble in aliphatic hydrocarbons and ether, but insoluble in fats, fixed oils, and mineral oil.

ETHYLCELLULOSE

Nonproprietary Names:

BP: Ethyl cellulose

PhEur: Ethylcellulosum

USPNF: Ethylcellulose

Synonyms: Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name: Cellulose ethyl ether

CAS Registry Number: [9004-57-3]

Empirical Formula and Molecular Weight: Ethylcellulose with complete ethoxyl substitution (DS = 3) is C12H23O6 (C12H22O5) *n*C12H23O5 where *n* can vary to provide a wide variety of molecular weight.

Functional Category: Coating agent; flavoring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Ethylcellulose is widely used in oral and topical pharmaceutical formulations

Use Concentration (%):

- Microencapsulation 10.0–20.0
- Sustained-release tablet coating 3.0–20.0
- Tablet coating 1.0–3.0
- Tablet granulation 1.0–3.0

The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules.

Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example, where granules are coated with ethylcellulose to inhibit oxidation.

Modified-release tablet formulations may also be produced using ethylcellulose as a matrix former. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films.

In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used.

- Ethylcellulose has been studied as a stabilizer for emulsions.
- Ethylcellulose is additionally used in cosmetics and food products.

Description:

Ethylcellulose is a tasteless, free-flowing, and white to light tan-colored powder.

Solubility:

Ethylcellulose is practically insoluble in glycerin, propylene glycol, and water. Ethylcellulose that contains less than 46.5% of ethoxyl groups is freely soluble in

chloroform, methyl acetate, and tetrahydrofuran, and in mixtures of aromatic hydrocarbons with ethanol (95%).

Ethylcellulose that contains not less than 46.5% of ethoxyl groups is freely soluble in chloroform, ethanol (95%), ethyl acetate, methanol, and toluene.

POLYMETHACRYLATES

Nonproprietary Names:

BP: Methacrylic acid–ethyl acrylate copolymer (1: 1)

PhEur: Acidum methacrylicum ethylis acrylas polymerisatum 1: 1

USPNF: Ammonio methacrylate copolymer,Methacrylic acid copolymer,
Methacrylic acid copolymer dispersion

Synonyms: *Acryl-EZE*; *Acryl-EZE MP*; *Eastacryl 30D*; *Eudragit*; *Kollicoat MAE 30 D*; *Kollicoat MAE 30 DP*; polymeric methacrylates.

Chemical Name, Trade Name and CAS Registry Number:

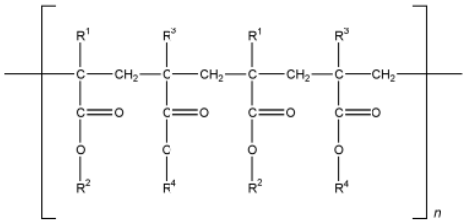
- Poly (methacrylic acid, methyl methacrylate) 1: 1 *Eudragit L100* [25806-15-1]
- Poly(butyl methacrylate, (2-dimethylaminoethyl)methacrylate, methyl methacrylate) 1 : 2 : 1 *Eudragit E100,Eudragit E12.5,Eudragit EPO* [24938-16-7].

Empirical Formula and Molecular Weight:

- *Eudragit L100* :Methacrylic acid–methyl methacrylate copolymer (1 : 1) is described in the PhEur 2005 as a copolymer of methacrylic acid and methyl methacrylate having a mean relative molecular mass of about 135 000.
- *Eudragit EPO:* The ratio of (2-dimethylaminoethyl) methacrylate groups to butyl methyacrylate and methyl methacrylate groups is about 2: 1: 1. Polyacrylate dispersion (30 per cent) is described in the PhEur 2005 as a

dispersion in water of a copolymer of ethyl acrylate and methyl methacrylate having a mean relative molecular mass of about 800 000.

Structural Formula:



Functional Category: Film former; tablet binder; tablet diluent

Applications in Pharmaceutical Formulation or Technology.

Type	**Supply form**	**Polymer dry weight content**	**Recommended solvents or diluents**	**Solubility/permeability**	**Applications**
Eudragit E12.5	Organic solution	12.5%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit EPO	Powder	98%	Acetone, alcohols	Soluble in gastric fluid to pH 5	Film coating
Eudragit L100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 6	Enteric coatings
Eudragit L100-55	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 5.5	Enteric coatings

Eudragit S100	Powder	95%	Acetone, alcohols	Soluble in intestinal fluid from pH 7	Enteric coatings
Eudragit RL 100	Granules	97%	Acetone, alcohols	High permeability	Sustained release

Description:

Polymethacrylates are synthetic cationic and anionic polymers of dimethylaminoethylmethacrylates, methacrylic acid, and methacrylic acid esters in varying ratios. Severaldifferent types are commercially available and may be obtained as the dry powder, as anaqueous dispersion, or as an organic solution. A (60: 40) mixture of acetone and propan-2-olis is most commonly used as the organic solvent.

Solubility:

Solubility of commercially available polymethacrylates in various solvents.

Type	**Acetone and alcohols**	**Dichloro-methane**	**Ethyl acetate**	**1 N HCl**	**1 N NaOH**	**Petroleum Ether**	**Water**
Eudragit E12.5	M	M	M	M	—	M	—
Eudragit S 100	S	I	I	—	S	I	I

Eudragit L 100	S	I	I	—	S	I	I
Eudragit RL 100	S	S	S	—	—	I	I

S = soluble; M = miscible; I = insoluble or immiscible; P = precipitates.

MANNITOL

Nonproprietary Names:

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitolum

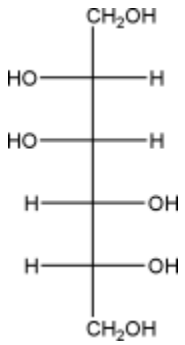
USP: Mannitol

Synonyms: Cordycepic acid; C*PharmMannidex; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.

Chemical Name and CAS Registry Number: D-Mannitol [69-65-8]

Empirical Formula and Molecular Weight: $C_6H_{14}O_6$ 182.17

Structural Formula:



Functional Category*:*

Diluent; diluent for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent

Applications in Pharmaceutical Formulation or Technology:

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients.

Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations.

Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and 'mouth feel'.

Description:

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth.

Solubility of Mannitol.

Solvent	**Solubility at 20°C**
Alkalis	Soluble

Solvent	Solubility at 20°C
Ethanol (95%)	1 in 83
Ether	Practically insoluble
Glycerin	1 in 18
Propan-2-ol	1 in 100
Water	1 in 5.5

MICROCRYSTALLINE CELLULOSE

Nonproprietary names:

BP: Microcrystalline cellulose (MCC)

JP: Microcrystalline cellulose

Ph Eur: Cellulosum microcrystallinum

USPNF: Microcrystalline cellulose

Synonyms: Avicel PH; Celex; Cellulose gel; Celphere; Ceolus KG; Crystalline cellulose; E460; Emcocel; Ethisphere; Fibro- cel; Pharmacel; Tabulose

.

Chemical name: Cellulose

Empirical formula: $C_6H_{10}O_5)_n$ Where n=220

Molecular weight: 36000

Functional category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrating agent.

Applications in Pharmaceutical Technology:

MCC is widely used in pharmaceuticals primarily as a binder /Diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. (20-90%)

It also has some lubricant and disintegrating properties. (5-15%).
It is used in cosmetics and food products.

Description:

MCC is purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. Commercially available in different particle sizes and moisture grades that have different properties and applications.

Solubility:

Slightly soluble in 5%w/v sodium hydroxide solution. Practically insoluble in water, dilute acids and most organic solvents.

CROSPOVIDONE

Nonproprietary names:
BP: Crospovidone
Ph Eur: Crospovidonum
USPNF: Crospovidone

Synonyms: Crosslinked povidone; E1202; Kollidon CL; Kollidon CL-M; Polyplasdone XL; Polyplasdone XL-10;
Chemical name: 1- Ethenyl-2-pyrrolidinone homopolymer
Emperical formula: $(C_6H_9NO)_n$
Molecular weight: >1000000.

Functional category: Tablet disintegrant

Applications in Pharmaceutical Technology:

1) Crospovidone is a water insoluble tablet disintegrant and dissolution agent used at 2-5%conc in tablets prepared by direct compression or dry granulation method.
2) It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels.
3) Studies suggest that particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide a faster disintegration than smaller particles.
4) Crospovidone can be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs.

Description: Crospovidone is a white to creamy white, finely divided free-Flowing, practically tasteless, and odorless or nearly odorless, hygroscopic powder.

Solubility: Practically insoluble in water and most organic solvents.

ASPARTAME

Nonproprietary names:

BP: Aspartame

Ph Eur: Aspartamum

USPNF: Aspartame

Synonyms: 3-Amino-N-(α-carboxyphenethyl) succinamic acid N-methyl ester; 3-Amino-N-(α- methoxycarbonyl phenethyl) succinamic acid; Aspartyl pheylamine methyl ester; Canderel; E 951; Equal; Methyl N-α-L-aspartyl-L- phenylalaninate; Nutrasweet; Sanecta; SC-18862; Tri-sweet.

Chemical name: N-α-L-Aspartyl-L-phenylalanine 1-methyl ester.

Emperical formula: $C_{14}H_{18}N_2O_5$

Molecular weight: 294.31

Functional category: Sweetening agent

Applications in Pharmaceutical Technology:

Aspartame is used as an intense sweetening agent in beverage products, food products, table top sweeteners and in pharmaceutical preparations including tablets, powder mixes and vitamin preparations.

It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180-200 times that of sucrose.

Therapeutically, aspartame is used in the treatment of sickle cell anemia.

Description: Aspartame occurs as an off white, almost odorless crystalline powder with an intensely sweet taste.

Solubility: Slightly soluble in ethanol (95%), sparingly soluble in water. At 20^0C the solubility is 1%w/v at the isoelectric point (pH 5.2). Solubility increases at higher temperatures and at more acidic pH, e.g. At pH 2 and 20^0C solubility is 10%w/v.

SODIUM BICARBONATE

Nonproprietary Names:

BP: Sodium bicarbonate

JP: Sodium bicarbonate

PhEur: Natrii hydrogenocarbonas

USP: Sodium bicarbonate

Synonyms: Baking soda; E500; Effer-Soda; monosodium carbonate; Sal de Vichy; sodium acid carbonate; sodium hydrogen carbonate.

Chemical Name and CAS Registry Number:

Carbonic acid monosodium salt [144-55-8]

Empirical Formula and Molecular Weight: $NaHCO_3$ 84.01

Structural Formula: $NaHCO_3$

Functional Category: Alkalizing agent; therapeutic agent

Applications in Pharmaceutical Formulation or Technology:

Sodium bicarbonate is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation.

In effervescent tablets and granules, sodium bicarbonate is usually formulated with citric and/or tartaric acid;

When the tablets or granules come into contact with water, a chemical reaction occurs, carbon dioxide is evolved, and the product disintegrates. Melt granulation in a fluidized bed dryer has been suggested as a one-step method for the manufacture of effervescent granules composed of anhydrous citric acid and sodium bicarbonate, for subsequent compression into tablets.

Uses of sodium bicarbonate.

Use	Concentration (%)
Buffer in tablets	10–40
Effervescent tablets	25–50
Isotonic injection/infusion	1.39

Solubility of sodium bicarbonate.

Solvent	Solubility at 20°C unless otherwise stated
Ethanol (95%)	Practically insoluble
Ether	Practically insoluble
Water	1 in 11
	1 in 4 at 100°C[a]
	1 in 10 at 25°C
	1 in 12 at 18°C

CITRIC ACID MONOHYDRATE

Nonproprietary Names:

BP: Citric acid monohydrate

JP: Citric acid

PhEur: Acidum citricum monohydricum

USP: Citric acid

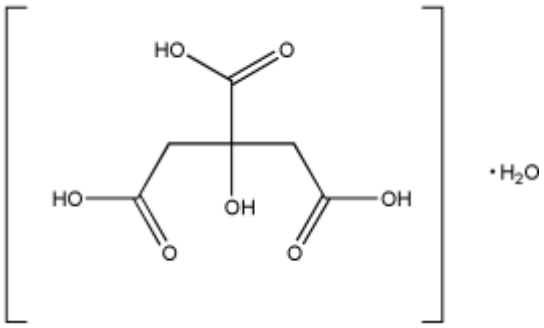
Synonyms: E330; 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

Chemical Name and CAS Registry Number:

2-Hydroxy-1,2,3-propanetricarboxylic acid monohydrate [5949-29-1]

Empirical Formula and Molecular Weight: $C_6H_8O_7 \cdot H_2O$ 210.14

Structural Formula:



Functional Category:

Acidifying agent; antioxidant; buffering agent; chelating agent; flavor enhancer.

Applications in Pharmaceutical Formulation or Technology:

Citric acid (as either the monohydrate or anhydrous material) is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions.

It has also been used experimentally to adjust the pH of tablet matrices in enteric-coated formulations for colon-specific drug delivery

Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets.

Description:

Citric acid monohydrate occurs as colorless or translucent crystals, or as a white crystalline, efflorescent powder. It is odorless and has a strong acidic taste. The crystal structure is orthorhombic.

Solubility:

Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.

COLLOIDAL SILICON DIOXIDE

Nonproprietary names: BP: Colloidal anhydrous silica

Ph Eur: Silica colloidalis anhydrica

USPNF: Colloidal Silicon Dioxide

Synonyms: Aerosil; Cab-O-Sil; Cab-O-Sil M-5P; Colloidal silica; Fumed silica light anhydrous silicic acid; Silicic anhydride; Silicon dioxide fumed; Wacker HDK.

Chemical name: Silica

Empirical formula: SiO_2

Molecular weight: 60.08

Functional category: Adsorbent; anti-caking agent; emulsion stabilizer; glidant; Suspending agent; tablet disintegrant; thermal stabilizer; viscosity increasing agent.

Applications in Pharmaceutical Technology:-

- It is used in pharmaceuticals, cosmetics and food products.
- It is used to stabilize emulsions and as a thixotropic thickening and suspending agent in gels and semisolid preparations.
- It is used to promote particulate suspension, eliminate, hard settling, and minimize the clogging of spray nozzles.
- It is used as a tablet disintegrant and as an adsorbent dispersing agent for liquids in powders.

Solubility: Practically insoluble in organic solvents, water and acids except hydrofluoric acid; soluble in hot solutions of alkali hydroxide forms a colloidal dispersion with water.

MAGNESIUM STEARATE

Nonproprietary names: BP: Magnesium Stearate

JP: Magnesium Stearate

Ph Eur: Magnesii stearas

USPNF: Magnesium Stearate

Synonyms: Magnesium octadecananoate; Octadecanoic acid; Magnesium salt; stearic acid magnesium salt.

Chemical name: Octadecanoic acid magnesium salt

Emperical formula: $C_{36}H_{70}MgO_4$

Molecular weight: 591.34

Functional category: Tablet and capsule lubricant.

Applications in Pharmaceutical Technology:-

Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations.

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 and 5%w/w.

It is also used in barrier creams.

Description: Magnesium stearate is a fine, white, precipitated or milled, Impalpable powder of low bulk density, having a faint odor or and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Solubility: Practically insoluble in ethanol, ethanol(95%), ether and water, slightly soluble in warm benzene and warm ethanol(95%).

RESULTS:

Drug- Compatibility Studies:

S.No	Ingredients	Ratio	Description		
			Initial	**55°C (2 weeks)**	**40±2°C /75±5 % RH (4 weeks)**
1	API	1	White	No change	No change
2	Avicel PH101	1	White	No change	No change
3	Crospovidone XL	1	White	No change	No change
4	Starch 1500	1	White	No change	No change
5	Etyl Cellulose 4CPS	1	white	No change	No change
6	PEG4000	1	Off white	No change	No change
7	Ethyl cellulose EPO	1	white	No change	No change
8	Mannozem	1	White	No change	No change
9	Magnesium stearate	1	White	No change	No change
10	Eudragit	1	White	No change	No change
11	Eudragit L100	1	White	No change	No change
12	Aerosil	1	white	No change	No change
13	Aspartame	1	Off white	No change	No change

14	Sodiumbicarbonate	1	White	No change	No change
15	Citric Acid	1	White	No change	No change
16	Mint Flavours	1	Off white	No change	No change
17	API+ Crospovidone XL	5:1	White	No change	No change
18	API+ Starch 1500	5:1	White	No change	No change
19	API+ MCC PH 101	1:5	Off white	No change	No change
20	API+PEG4000	5:1	Off white	No change	No change
21	API+ EC 4CPS	5:1	Off white	No change	No change
22	API+ Aerosil	5:1	White	No change	No change
23	API+ MS	5:1	Off white	No change	No change
24	API+EC EPO	5:1	Off white	No change	No change
25	API+Mannozem	5:1	Off white	No change	No change
26	API+Eudragit EPO	5:1	White	No change	No change
27	API+Eudragit L100	5:1	Off white	No change	No change
28	API+Aspartame	5:1	Off white	No change	No change
29	API+SB	5:1	Off white	No change	No change
30	API+ Citric Acid	5:1	Off white	No change	No change
31	API+ Mint	5:1	White	No change	No change

Physical Parameters of API.

S.No.	Test	Specifications	Results
1.	Description	Off-white to beige colored powder.	Complies
2.	Solubility	Soluble in water, slightly soluble in chloroform.	Complies
3.	Identification: IR-Spectrum	IR-Spectrum of the test sample should match with the IR-Spectrum of the working standard.	Complies
4.	Loss on Drying (at 105 °C for 3hrs)	0.14% w/w	≯ 0.5% w/w
5.	Residue on ignition	0.04% w/w	≯ 0.1% w/w
6.	Related substances (by HPLC) Impurity-A Impurity-B Any other impurity Total Impurities	 Not detected Not detected 0.09% 0.19%	 ≯ 0.15 ≯ 0.15 ≯ 0.10 ≯ 1.00
7.	Assay	99.9% w/w	≮ 98.0% w/w & ≯ 102.0% w/w. calculated on dried substance.

*[Impurity-A: 3-(2-Chloroethyl)-6, 7, 8, 9-tetrahydro-9-hydroxy-2-methyl-4H pyrido (1,2-a)pyrimidine-4-one.

Impurity-B: 6-fluoro-3-piperidin-4-yl-1,2-benzisoxazloe.

PARTICLE SIZE ANALYSIS.

S.No.	ASTM	Weight of mesh(A)	Weight of mesh+Powder (B)	B-A	%Retained
1	100	331.9	349.2	17.3	57.66
2	140	325.8	332.2	6.4	21.33
3	200	324.1	326.4	2.3	7.66
4	Collector	539.9	543.9	4.0	13.33
Total				30.0	99.98

***Note:** Powder taken = 30 gms.

$$\%\text{Retained} = \frac{\text{B-A}}{\text{Weight of powder taken}} \times 100$$

DRUG SOLUBILITY STUDY (pH 1-7).

S.No.	Medium	Percentage	Mg/ml
1	D.M.Water	100.9%	0.37
2	0.1N HCl	101.5%	0.37
3	4.5 Acetate buffer	100.1%	0.36
4	6.8 Phosphate buffer	100.1%	0.36

pH:

60 mg of API in 50 ml of DM Water.

pH of API = 7.92

2 Tablets in 50 ml of DM Water.

pH of tablets = 6.12

Innovators 2 Tablets in 50 ml of DM Water.

pH of tablets = 6.65

Density:

Initial weight	=	25.9 gms
Initial volume	=	88 ml
Tapped density	=	0.728 gm/ml
Bulk density	=	0.521 gm/ml
Compressibility Index	=	28.40 %
Hausner Ratio	=	1.397

Dissolution parameters:

Apparatus	:	USP2, Paddle.
Medium	:	22M sodium acetate buffer, pH.4.5.
Medium volume	:	500 ml.
Medium Temp	:	37 ±0.5 °C.
Paddle speed	:	50 rpm.
Sampling Time	:	60 min
Sampling Time Points (profile)	:	5, 15, 30, 40, 60 min.
Sampling volume	:	5 ml

Chromatographic conditions for Dissolution and Assay:

Column	:	Kromosil C18, (150×4.6mm), 5µm.
Flow rate	:	1.0ml/min
Wave length	:	UV-254

Column Temperature: 30°C

Injection volume : 20µl

Run time : 15min

UNITARY FORMULA

Label claim: Each tablet contains: Prednisolone sodium phosphate 42.98mg Equivalent to Prednisolone 30mg.

Materials	**Percentage in a tablet**	**Function**
Prednisolone sodium phosphate	7.16	Active Pharmaceutical Ingredient
Avicel PH101	33.33	Diluent
Poly ethylene Glycol 4000	7.16	Taste masking agent
Ethyl cellulose 4CPS	7.16	Taste masking agent
Ethyl cellulose	2.5	Taste masking agent
Mannozem EZ (Mannitol spray dried)	20.55	Sweetener
Eudragit EPO	3.58	Taste masking agent
Eudragit L100	3.58	Taste masking agent
Crospovidone XL-10	12.50	Disintegrant
Aspartame	4.16	Sweetener
Sodium Bicarbonate	2.66	Alkalizing agent
Citric acid	2.08	Buffering agent

Magnesium stearate	1.90	Lubricant
Aerosil	0.47	Glident
Mint flavors	0.83	Flavor

formulation 1:- For 1000 Tablets.
Preparation of *drug-stearic acid solution*:

Weigh accurately the required quantity of API and dissolve in 129ml of water. Weigh accurately the required quantity of Stearic acid and dissolve in 200ml of IPA. Then mix drug solution to stearic acid solution. Solubilise with continuous stirring for homogenous mixing for 20min.

Granulation:

Weigh Mannozem EZ, Crosspovidone XL, Avicel pH101, and Starch1500. Then sift all the ingredients through 30# mesh. Take all ingredients in a bowl and then granulate with the help of drug-stearic acid solution to form a damp mass. Then granules are kept for drying until dried. Dried granules are passed through 35# mesh.

Weigh Sodium bicarbonate, Citric acid, Aspartame, Mint flavor, Aerosil, Sodium stearyl fumarate are pass through 35# mesh and mix to the granules, one by one in a continuous manner. Mix the blend continuously for 3min.

Observation:

Powder taste is bitter.

Formulation 2:- For 200 Tablets.

Weigh accurately the required quantity of ***Ethylcellulose*** and add 20gms of IPA, stir for 45min, by using mechanical stirrer to get clear solution. Weigh accurately the required quantity of API and dissolve in required quantity (25ml) of water to get clear solution. Weigh accurately Avicel pH101 and passed through 40#

FORMULATION OF PREDNISOLONE ODT (30mg)

Intragranulation (mg/tab)

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
API	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98	42.98
Poly Ethylene Glycol 4000	__	—	—	—	40	40	42.98	42.98	42.98	42.98	42.98	42.98	__
Ethyl cellulose 4cps	—	—	—	—	—	—	—	25	—	—	40	__	42.98
Purified water	Q.S.	Q.S.	Q.S.	__	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	__
Ethyl cellulose	__	10	__	12	15	—	—	—	—	—	—	—	—
Isopropyl alcohol	Q.S.	Q.S.	—	—	Q.S.	Q.S.	—	—	—	—	Q.S.	__	Q.S.
Methylene chloride	—	—	—	—	Q.S.	Q.S.	—	—	—	—	—	—	—
MCC (Avicel pH101)	100	250	250	248	245	245	225	230	230	230	230	230	200
Aspartame	—	—	—	—	—	—	10	10	10	10	10	10	10
Mannozem. EZ (spray dried mannitol)	244.02	—	—	—	—	—	60	60	60	60	60	60	__
Eudragit L100	—	—	—	—	—	—	—	—	21.49	14.32	__	21.49	21.49
Eudragit EPO	—	—	42.98	—	—	42.98	42.98		21.49	28.64	40	21.49	21.49
Isopropyl alcohol	—	—	Q.S.	Q.S.	—	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.

Acetone	—	—	Q.S.	Q.S.	—	Q.S.	Q.S.	__	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Stearic acid	40	—	—	—	—	—	—	—	—	—	—	—	—
Starch 1500	40	—	—	—	—	—	—	—	—	—	—	—	—
Crosspovidone XL	60	—	—	—	—	—	—	—	—	—	—	—	75

Extra Granulation (mg/tab)

Ingredients	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**	**F13**
Mannozem. EZ (spray dried mannitol)	—	182.25	152.29	182.25	137.27	109.29	56.31	69.13	*51.40*	51.40	14.29	*33.31*	123.31
Crosspovidone XL 10	—	57	57	57	57	57	57	57	*57*	57	57	*75*	75
Sodium bicarbonate	15	16	16	16	16	16	16	16	16	16	16	16	16
Citric acid	20	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5	12.5
Aspartame	18	10	10	10	15	15	15	15	15	15	15	15	15
Mint flavor	2	5	2	5	5	5	5	5	5	5	5	5	5

Aerosil (colloidal silicon dioxide)	6	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85	2.85
Magnesium stearate	__	11.40	11.40	11.40	11.40	11.40	11.40	11.40	11.40	11.40	11.40	11.40	11.40
Sodium stearyl fumarate	12	—	—	—	—	—	—	—	—	—	—	—	—
Total(mg)	600	600	600	599.98	600	600	600	599.84	600	600	600	600	600

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mesh. And granulate with drug solution to get a wet mass. The wet mass is dried in tray drier at 60^{o}C.

After 15 min the same wet mass was again granulated with ethyl cellulose solution. The wet mass was passed through 10# mesh and dried at 40^{o}C. The dried granules are passed through 20# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor and pass through 40# mesh. Add to the dried granules and mix for 5min. Weigh accurately Magnesium stearate, Aerosil and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

Powder taste is bitter.

Formulation 3:- For 500 Tablets.

Weigh accurately the required quantity of API and dissolve in required quantity (63ml) of water to get clear solution. Weigh accurately ***Eudragit EPO*** are add to the mixture of (1:1) IPA and Acetone, stir for 45min using mechanical stirrer to get clear solution.

Weigh accurately Avicel pH101 and pass through 40# mesh. Granulate with drug solution to get a wet mass. The wet mass is dried in tray drier at 60^{o}C.

Semi-dried granules are granulating with Eudragit EPO solution. The wet mass is passed through 10# mesh and dried at 45^{o}C. The dried granules are passed through 18# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor and pass through 40# mesh. Add to the dried granules and

mix for 5min. Weigh accurately Magnesium stearate, Aerosil and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 4:- For 200 Tablets.

Weigh accurately the required quantity of ***Ethylcellulose*** and add to the 20gms of IPA, stir for 45min, by using mechanical stirrer to get clear solution. Weigh accurately the required quantity of API and dissolve in required quantity (63ml) of water to get clear solution.

Weigh accurately Avicel pH101 and pass through 40# mesh. Granulate with drug solution to get a wet mass. The wet mass is dried in tray drier at 60^{o}C. Semi-dried granules are granulated with Ethyl cellulose solution. The wet mass passed through 12# mesh and dried at 60^{o}C. The dried granules are passed through 18# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor, and Aerosil are passed through 40# mesh. And add to the dried granules and mix for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 5:- For 200 Tablets.

Weigh accurately the required quantity of API and dissolve in required quantity (25ml) of water to get clear solution. Weigh accurately Avicel pH101 and pass through 40# mesh. Granulate with drug solution to get a wet mass. The wet mass is dried in tray drier at 55±5 ^{o}C.

Weigh accurately ***PEG4000*** and add to the required quantity of mixture of IPA and Methylene chloride (1:1) (13:13) solution to get a clear solution. The dried granules are granulated with PEG4000 solution. The wet mass is dried in tray drier at 55±5 ^{o}C.

The dried granules are passed through 40# mesh. Weigh accurately Ethyl cellulose and add to the 20gms of IPA, stir for 45min, by using mechanical stirrer to get cleat solution. The above granules are again granulated with Ethyl cellulose solution. The wet mass was passed through 12# mesh and dried at 55±5 ^{o}C.

The dried granules are passed through 18# mesh. Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor, and Aerosil and pass through 40# mesh. Add to the dried granules and mixed for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 6:- For 200 Tablets.

Weigh accurately the required quantity of API and dissolve in required quantity (25ml) of water to get clear solution. Weigh accurately Avicel pH101 and passed through 40# mesh. Granulate with drug solution to get a wet mass. The wet mass is dried in tray drier at 55±5 ^{o}C.

Weigh accurately ***PEG4000*** and add to the required quantity of mixture of *IPA* and *Methylene chloride (1:1) (13:13)* solution to get a clear solution. The dried granules are granulated with PEG4000 solution. The wet mass is dried in tray drier at 55±5 ^{o}C.

The dried granules are passed through 40# mesh. Weigh accurately ***Eudragit EPO*** and add to the mixture of *(1:1) IPA* and *Acetone*, stir for 45min using mechanical stirrer to get clear solution. The above granules are granulated with Eudragit EPO solution. The wet mass was passed through 12# mesh and dried at 55±5 ^{o}C. The dried granules are passed through 18# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor and Aerosil and pass through 40# mesh. Add to the dried granules and mix for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter.

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 7:- For 200 Tablets.

Weigh accurately ***PEG4000*** are added to the required quantity of water (45gms). Weigh accurately API and add it to the above solution. Mix for 10min to get a clear solution. Weigh Avicel pH101, Mannozem EZ and Aspartame and pass through 40# mesh and granulate with the above solution.

The wet mass was passed through 12# mesh and dried at 55±5 ^{o}C. The dried granules are passed through 12# mesh. Weigh accurately ***Eudragit EPO*** and add to the mixture of *(1:1) IPA* and *Acetone*, stir for 30min using mechanical stirrer to get clear solution.

The above granules are granulated with Eudragit EPO solution. The wet mass was passed through 12# mesh and dried at 55±5 ^{o}C. The dried granules are passed through 40# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor, and Aerosil are passed through 40# mesh and added to the dried granules and mixed for 3min.

Weigh accurately Magnesium stearate and passed through 40# mesh, and added to the above blend and lubricated for 2min.

Observation:

After taste is bitter.

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 8:- For 200 Tablets.

Weigh accurately ***PEG4000*** and added to the required quantity of water (45gms). Weigh accurately API and add it to the above solution. Mixed for 10min to get a clear solution. Weigh Avicel pH101, Mannozem EZ and Aspartame and pass through 40# mesh and granulate with the above solution.

The wet mass was passed through 12# mesh and dried at 55±5 ^{o}C. The dried granules are passed through 12# mesh. Weigh accurately ***Ethylcellulose*** and add to the required quantity of (25gms) IPA. Stir for 45min using mechanical stirrer to get clear solution.

The above granules are again granulated with Ethyl cellulose solution. The wet mass passes through 12# mesh and dried at 55±5 ^{o}C. The dried granules are passed through 40# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor and Aerosil and pass through 40# mesh. Add to the dried granules and mix for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter.

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 9 and 12:- For 500 Tablets.

Weigh accurately ***PEG4000*** and add to the required quantity of water (113.75gms). Weigh accurately API and add it to the above solution. Mix for 10min to get a clear solution. Weigh Avicel pH101, Mannozem EZ and Aspartame and pass through 40# mesh and granulate with the above solution.

The wet mass was passed through 12# mesh and dried at 60^{o}C. The dried granules are passed through 30# mesh.

Weigh accurately ***Eudragit EPO,Eudragit L100 (1:1)*** and add to the mixture of (1:1) (50:50) IPA and Acetone, stir for 45min using mechanical stirrer to get clear solution. The above granules are again granulated with above (step5) solution. The wet mass was passed through 12# mesh and dried at 55 ± 5^{o}C. The dried granules are passed through 30# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor and Aerosil and pass through 40# mesh. Add to the dried granules and mix for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter.

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 10:- For 500 Tablets.

Weigh accurately ***PEG4000*** and add to the required quantity of water (113.75gms). Weigh accurately API and add it to the above solution. Mix for 10min to get a clear solution. Weigh Avicel pH101, Mannozem EZ and Aspartame and pass through 40# mesh and granulate with the above solution. The wet mass was passed through 12# mesh and dried at 60^{o}C. The dried granules are passed through 30# mesh.

Weigh accurately ***Eudragit EPO,Eudragit L100 (2:1)*** and added to the mixture of (1:1) (50:50) IPA and Acetone, stirred for 45min using mechanical stirrer to get clear solution. The above granules are again granulated with above (step5) solution. The wet mass was passed through 12# mesh and dried at 55±5^{o}C. The dried granules are passed through 30# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor, and Aerosil and passed through 40# mesh. Add to the dried granules and mix for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter.

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 11:- For 500 Tablets.

Weigh accurately ***PEG4000*** and add to the required quantity of water (113.75gms). Weigh accurately API and add it to the above solution. Mix for 10min to get a clear solution. Weigh Avicel pH101, Mannozem EZ and Aspartame and pass through 40# mesh and granulate with the above solution. The wet mass was passed through 12# mesh and dried at 60^{o}C. The dried granules are passed through 30# mesh.

Weigh accurately ***Ethyl cellulose*** and add to the required quantity of (100gms) IPA and stir for 45min using mechanical stirrer to get clear solution. The above granules are again granulated with above solution. The wet mass was passed through 12# mesh and dried at 55±5^{o}C. The dried granules are passed through 30# mesh.

Weigh accurately ***Eudragit EPO*** and add to the mixture of *(1:1) IPA* and *Acetone*, stir for 45min using mechanical stirrer to get a clear solution. The above granules are again granulated with above solution. The wet mass was passed through 12# mesh and dried at 55±5^{o}C. The dried granules are passed through 30# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor and Aerosil and pass through 40# mesh. Add to the dried granules and mix for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter.

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

Formulation 13:- For 500 Tablets.

Weigh accurately ***Ethyl cellulose*** and API and pass through 40# mesh and mix well. And granulate with required quantity of (17) IPA to get wet mass. The wet mass was passed through 12# mesh and dried at 50±5 ^{o}C. The dried granules are passed through 30# mesh. Weigh Avicel pH101 and Aspartame are passed through 40# mesh and add to the above dried granules and mixed for 5min.

Weigh accurately ***Eudragit EPO, Eudragit L100 (1:1)*** and add to the mixture of (1:1) (50:50) IPA and Acetone. The above blend is granulated with above solution to get wet mass. The wet mass was passed through 12# mesh and dried at 50±5 ^{o}C. The dried granules are passed through 30# mesh.

Weigh Mannozem EZ, Crosspovidone XL10, Sodium bi carbonate, citric acid, Aspartame, Mint flavor and Aerosil and pass through 40# mesh. Add to the dried granules and mix for 3min.

Weigh accurately Magnesium stearate and pass through 40# mesh, and add to the above blend and lubricate for 2min.

Observation:

After taste is bitter.

Compression:

Lubricated granules are compressed with 12.5mm round flat punches with scale line on, one punch was used for compression.

RESULTS AND DISCUSSION

EVALUATION OF TABLETS:

Formulation	Avg.Weights(mg)	Thickness (mm)	Hardness kg/cm^2)	Friability (%)	Disintigration Time (sec)
F-3	602.6	4.72	4.14	1.43	22
F-4	602.5	4.72	3.40	1.40	24
F-5	606.3	4.75	3.90	1.13	40
F-6	604.1	4.90	3.58	1.00	28
F-7	604.2	4.88	3.86	1.43	56
F-8	604.7	3.90	3.98	1.54	45
F-9	600.3	5.13	3.02	2.08	25
F-10	601.6	5.13	2.69	1.89	21
F-11	600	5.11	3.10	2.30	30
F-12	600.1	5.14	3.11	1.87	26
F-13	601.9	4.70	4.05	0.72	26

Taste evaluation (Palatability study) for formulation containing mint flavor:

S.No.	Volunteers	AGE	SEX	Patient acceptability (Taste)		
				Good	Better	Average
1.	Volunteer 1	26	M	√		
2.	Volunteer 2	24	F	√		
3.	Volunteer 3	28	M	√		
4.	Volunteer 4	30	M			√
5.	Volunteer 5	27	F	√		
6.	Volunteer 6	25	M	√		
7.	Volunteer 7	31	M		√	
8.	Volunteer 8	29	M	√		
9.	Volunteer 9	35	M	√		
10.	Volunteer 10	24	F		√	

DISSOLUTION PROFIE OF ORAPRED ODT (30mg)

Time (min)	%Drug release in Water	Time (min)	%Drug release in 0.1N HCl	% Drug release in 4.5 Acetate buffer
0	0	0	0	0
5	36.7	5	47.6	80.9
10	49.9	15	89.2	97.6
20	68.5	30	94.4	99.6
30	71.1	45	95.6	98.6
45	81.1	60	96.3	99.2
Assay	*88.9*		*98.6*	*99.4*

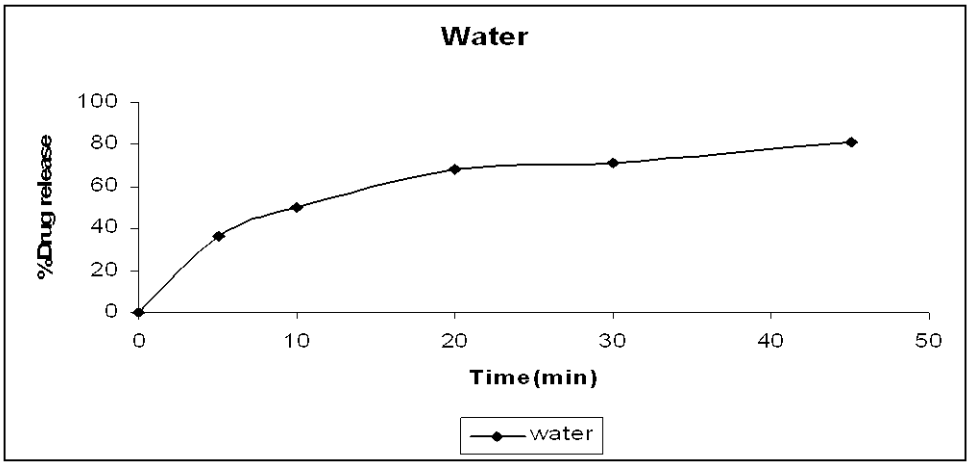

Figure 1: Dissolution profile of ORAPRED ODT in Water.

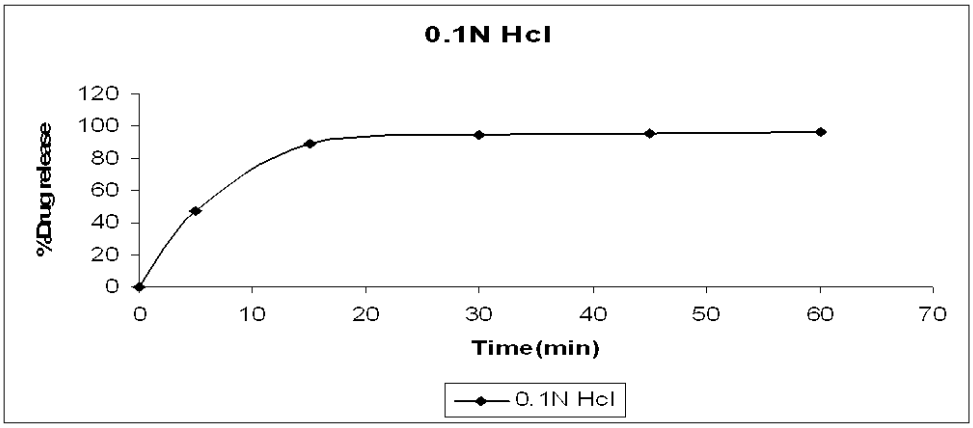

Figure 2: Dissolution profile of ORAPRED ODT in 0.1N Hcl.

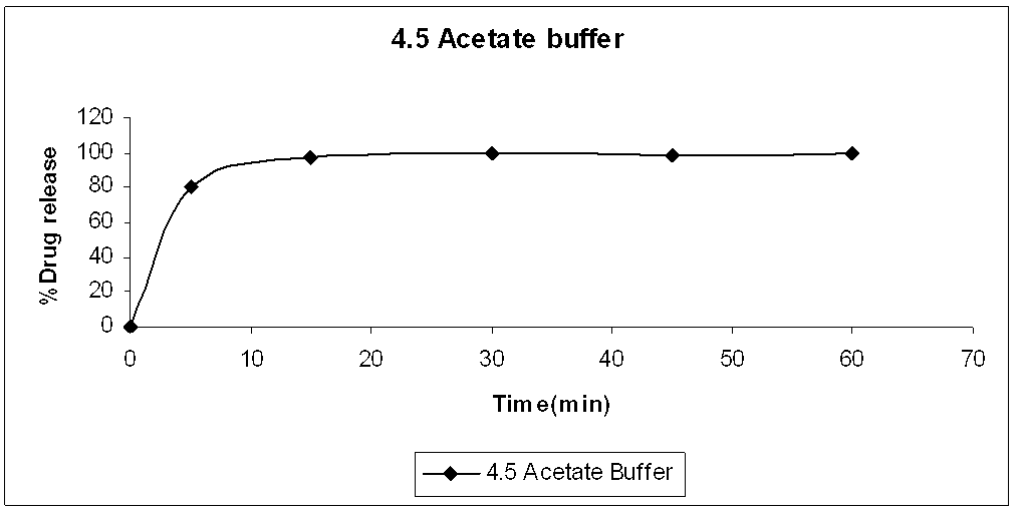

Figure 3: Dissolution profile of ORAPRED ODT in 4.5 Acetate buffer.

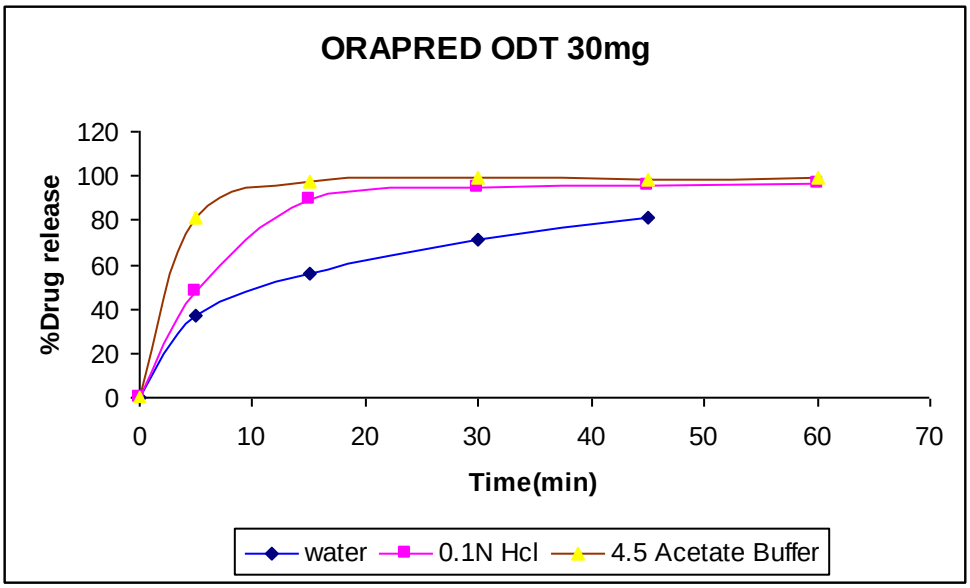

Figure 4: Dissolution profile of ORAPRED ODT in different media.

Cumulative Percentage Of Drug Release in *pH 4.5 Phosphate Buffer*.

Sampling Time	Cumulative Percentage Of Drug Release in *pH 4.5 Phosphate Buffer*.					
	F-3	F-4	F-5	F-6	F-7	F-8
5	96.3	110.6	103.5	103.5	101.8	99.1
15	100.1	111.0	105.9	105.9	102.2	99.2
30	100.8	110.8	106.6	106.6	102.4	106.1
45	101.3	110.6	107.3	107.3	102.4	106.5
60	101.2	110.0	107.8	107.8	102.4	107.4
Assay	*100.7*	*109.7*	*106.2*	*101.9*	*100.6*	*104.9*

Sampling Time	Cumulative Percentage Of Drug Release in *pH 4.5 Phosphate Buffer*.				
	F-9	F-10	F-11	F-12	F-13
5	73.2	74.2	48.5	65.3	60.3
15	87.4	84.6	76.1	86.7	78.7
30	91.7	89.8	80.6	92.2	89.1
45	95.8	95.2	80.6	95.7	92.4
60	95.0	93.3	87.5	99.4	98.1
Assay	*89.0*	*88.8*	*80.1*	*99.7*	*99.2*

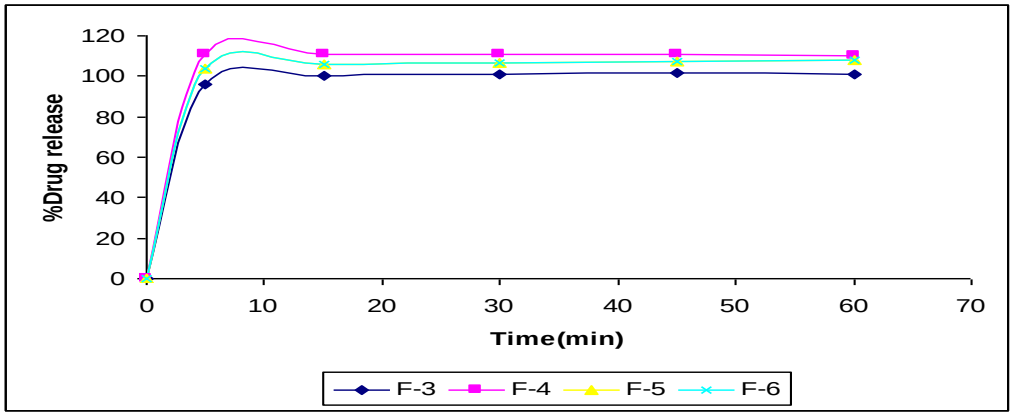

Figure 5: Dissolution profile of Formulations F-3, F-4, F-5, and F-6.

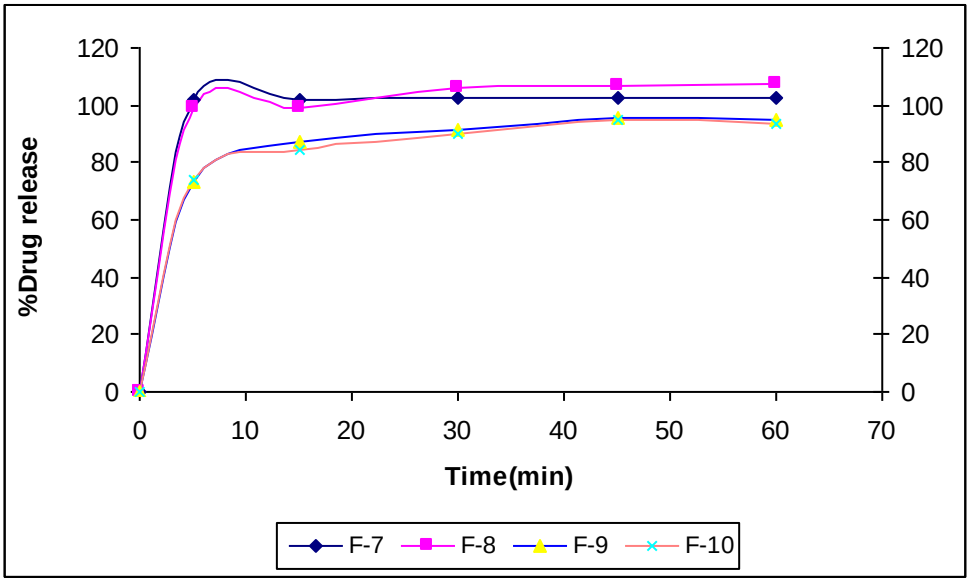

Figure 6: Dissolution profile of Formulations F-7, F-8, F-9, and F-10.

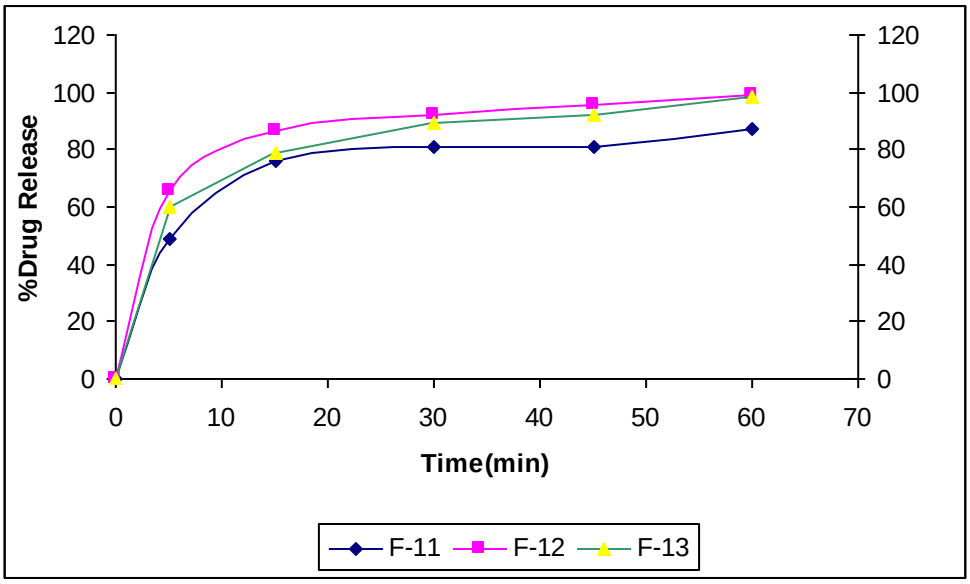

Figure 7: Dissolution profile of Formulations F-11, F-12, and F-13.

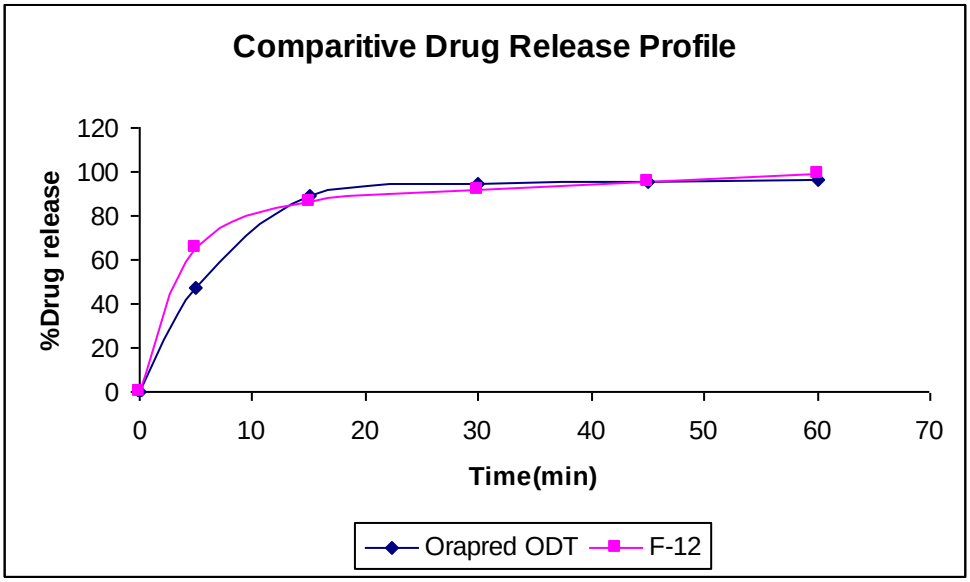

Figure 8: Dissolution profile of ORPRED and Formulation F-12.

DISCUSSION

The present investigation was undertaken to formulate Prednisolone into orally disintegrating tablet formulation for the treatment of severe inflammatory conditions allergies, arthritis, asthma, or skin reactions.

Wet granulation techniques were used in formulating the drug into orally disintegrating tablet.

All the experimental formulation batches have been subjected to various evaluations viz, average weight, friability, disintegration, thickness, hardness, dissolution, content uniformity and taste masking.

Formulation F-1 was made by wet granulation using Drug-stearic acid solution and the lubricated blend taste has not met the specifications of ODT.

Formulation F-2 was made by wet granulation using Ethylcellulose(1.66%) in Isopropyl alcohol as a taste masking agent and the lubricated blend taste has not met the specifications of ODT.

Formulation F-3 was made by wet granulation using Eudragit EPO (7.16%) {in Isopropyl alcohol and acetone (1:1)} as a taste masking agent and the lubricated blend had good taste. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-4 was made by wet granulation using Ethylcellulose (2.0%) {in Isopropyl alcohol} as a taste masking agent and the lubricated blend after taste was bitter. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-5 was made by wet granulation using PEG4000 (6.66%) {in Isopropyl alcohol and methylene chloride} as a taste masking agent, drug has to be dissolved in water and granulated with mcc and again granulated it with PEG4000 solution.

And the dried granules were again granulated with Ethylcellulose (2.5%) {in Isopropyl alcohol} solution and extra granulation was carried out and the lubricated blend after taste was bitter. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-6 was made by wet granulation using PEG4000 (6.66%) {in Isopropyl alcohol and methylene chloride} as a taste masking agent, API has to be dissolve in water and granulate with mcc and again granulate it with PEG4000 solution.

And the dried granules were again granulated with Eudragit EPO (7.16%) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend after taste was bitter. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-7 was made by using PEG4000 in required quantity of water and API was added to PEG4000 solution granulation was done with mcc, mannitol i.e., mannogem EZ and Aspartame. And granulated with Eudragit EPO (7.16%) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend after taste was bitter. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-8 was made by replacing Eudragit EPO solution with Ethylcellulose 4cps (4.16%) (in Isopropyl alcohol) solution and the remaining ingredients are same as formulation F-7. And the lubricated blend after taste was bitter. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-9, 10 &11 was made by using PEG4000 in water, API was added to it to get a clear solution granulation was done with mannogem EZ and Aspartame.

For F-9 granulate the above granules with Eudragit L100 and Eudragit EPO(1:1)(3.58:3.58) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend had good taste. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-10 granulate the above granules with Eudragit L100 and Eudragit EPO(1:2)(4.77:2.38) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend has good taste. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-11 granulate the above granules with Ethylcellulose 4cps(6.66) in IPA and dried granules were again granulated with Eudragit EPO(6.66) {in Isopropyl alcohol and acetone (1:1)} solution and extra granulation was carried out and the lubricated blend had good taste. In this formulation hardness and disintegration gave satisfactory results.

Formulation F-12 was reproducibility of F-9 Batch with change in percentages of mannozem EZ (5.55%) and crosspovidone XL10 (12.5%) and lubricated blend has good taste. In this formulation hardness and disintegration gave satisfactory results.
Formulation F-13 was made by Ethylcellulose4cps and API are mixed and granulated with Isopropyl alcohol and after mixing the remaining intra granular ingredients and granulating with Eudragit L100 and Eudragit EPO(1:1){in Isopropyl alcohol and acetone (1:1)} solution. Extra granulation was carried out and the lubricated blend had a good taste.

SUMMARY AND CONCLUSION

The demand for orally disintegrating tablets has enormously increased during the last decade. Particularly for geriatric and pediatric patients who have difficulty in swallowing conventional tablets and capsules. Oral administration of the drugs is difficult in patients having concomitant vomiting or diarrhea. Fast dissolving or fast disintegrating dosage form is advantageous for such patients. Fast dissolvable or fast disintegrating dosage forms are meant to disintegrate immediately upon contact with the saliva leading to faster release of drug in the oral cavity. Because administrating the fast disintegrating dosage forms, absorption of the drugs occurs through buccal mucosa and it may reduce the first pass metabolism leading to better efficacy of the drug.

Prednisolone is a naturally occurring glucocorticoids (hydrocortisone), it targets to corticosteroid binding globulin (it regulates Enzyme regulatory activity, Enzyme inhibitory activity and protease inhibitory activity. Which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems. Used in treatment of severe inflammatory conditions including allergies, arthritis, asthma, or skin reactions.

Its metabolizing enzyme is Cytochrome P450 3A4 (CYP 3A40). In present work wet granulation technique was employed to prepare tablets. Microcrystalline cellulose was used as diluent. Aspartame and mannitol were used as sweetening agents. Crospovidone XL10 as disintegrant. Predinisolone Sodium Phosphate was having bitter taste and to mask the bitter taste flavoring agent like mint flavour and taste masking agents like PEG4000, Ethylcellulose 4cps, Eudrait EPO and Eudragit L100 were used. Post compressional parameters hardness, friability, weight variation, disintegration time, drug content and dissolution studies are studies were done.

Taste, disintegration and dissolution profiles of best formulations F-12 and F-13 are better than marketed product i.e. ORAPRED.

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